Risk Factors for Abdominal Aortic Aneurysm and Larger Infrarenal Aortic Diameters in a General Population

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DEDICATION

This dissertation is dedicated to my parents, my husband and my daughter for their support and unconditional love.

ABSTRACT

Abdominal aortic aneurysms (AAAs) comprise an important public health issue, which could be reduced by primary prevention. Identifying AAA risk factors is critical for developing effective preventive strategies. Previous epidemiologic studies have suggested that some risk factors for atherosclerotic cardiovascular disease are also associated with increased risk of incident AAAs, including advanced age, male gender, white race, greater height, smoking, hypertension, dyslipidemia, and some biomarkers related to inflammation and hemostasis. Some observational studies showed an inverse relationship between diabetes and AAA; while others did not show an association. The inverse relationship between diabetes and AAA is considered counterintuitive in the context of diabetes being a risk factor for various cardiovascular diseases. To better understand the etiology of AAA, further investigation on the relation between atherosclerosis and AAA is warranted. Also, the relation between diabetes and AAA needs to be studied further.

With the exception of screening studies where AAAs were defined commonly as a maximum infrarenal aortic diameter (IAD) ≥ 3 cm, in most existing epidemiologic studies, AAAs were obtained through medical records and death certificates. This approach ascertains clinical AAAs that were either symptomatic or at least clinically detected. However, large screening studies have suggested that most AAAs are asymptomatic, even though aortic size often expands rapidly and many asymptomatic AAAs may eventually become

symptomatic. Furthermore, an increased IAD between 2.3 and 3 cm has been associated with higher risk of future AAA and other cardiovascular events. Thus, examining the determinants of elevated IADs (i.e. IAD ≥ 2.2) among individuals without clinical or asymptomatic AAAs is potentially important to the prevention of AAAs.

Manuscript 1 examined the associations of carotid atherosclerosis and stiffness with later AAAs in ARIC. We used carotid intima-media thickness (1987-1992) and atherosclerotic plaque (1987-1989) as indices of carotid atherosclerosis, and used carotid Beta Index (1990-1992) to represent carotid distensibility. We identified 542 incident, clinical AAAs during follow-up through 2011 using hospital discharge codes, Medicare outpatient diagnoses, or death certificates during 22.5 years of follow-up. After multivariable adjustment, the presence of carotid atherosclerotic plaque at baseline was associated with 1.31 (95% CI: 1.10 - 1.57; P: 0.003) times higher risk of clinical AAA. Greater carotid intima-media thickness and Beta Index were also associated with clinical AAA with a dose-response across quartiles (P trend for both: 0.006; hazard ratios [95% CI] for the highest vs. lowest quartiles: 1.55 [1.13 - 2.11] and 1.68 [1.16 - 2.43], respectively). The results suggest that indices of greater carotid atherosclerosis and lower carotid distensibility are markers of increased AAA risk.

Manuscript 2 explored risk factors for an elevated IAD (IAD ≥ 2.2 cm) in the absence of AAA in 5620 ARIC participants who attended an abdominal ultrasound screening in 2011-2013. We assessed a variety of risk factors and

created derived variables to capture their long-term cumulative effects (over 1987-2013). In the model with adjustment for AAA risk factors, men (vs. women) had 2.50 (95% CI: 1.90, 3.28) times higher odds of having an elevated IAD, and participants with long-term diabetes (vs. non-diabetics) had 0.52 (0.35, 0.77) times lower odds. Height, waist circumference and smoking pack-years were positively associated with elevated IADs [ORs (95% CI) for the highest vs. lowest quintiles of each risk factor: 1.93 (1.36, 2.75), 1.67 (1.28, 2.19) and 1.62 (1.26, 2.08), respectively]. Other factors were not associated with elevated IAD. In summary, male sex, smoking, greater height, larger waist circumference and not having diabetes were associated with elevated IAD among persons without an AAA. The findings highlight the potential for primary prevention of AAA through control of these factors.

Manuscript 3 represents a meta-analysis of prospective cohort studies and case-control studies to examine further the relation between diabetes and AAAs. We searched for English literature from online database search (MEDLINE (1966-), EMBASE and Web of Science) plus a manual examination of references in selected articles as of Feb 2018, and included a total of 12 cohorts with 11,410 AAAs in 2,665,121 adult participants and 4 case-control studies with 1,065 AAAs and 12,074 controls who met pre-determined eligibility criteria in the meta-analyses. A DerSimonian and Laird random effects model pooled association estimates and their 95% confidence intervals from studies. Diabetes was inversely associated with the risk of AAA (pooled relative risk: 0.56; 95%

confidence interval: 0.50 - 0.63). Results were similar in the subgroup analyses by sex (male/female), setting (population/clinical), and study design (cohort/case-control). In summary, in contrast with diabetes being a risk factor for most cardiovascular diseases, diabetes appears to be strongly and inversely associated with the risk of AAA.

In summary, my dissertation studies filled a gap of literature and further assessed AAA etiology by completing the three manuscripts. The three studies have potential to improve understanding of the etiology and early prevention of AAAs at the population level. Findings from my dissertation studies may offer a strategy to clinically identify high-risk individuals.

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Chapter 1. Introduction and Literature Review

1.1 Abdominal aortic aneurysm (AAA) is an important public health issue

An abdominal aortic aneurysm (AAA) is a weakening in the wall of the abdominal aorta. The large amount of blood that flows through puts pressure on the weak spot, resulting in the formation of an AAA. A large proportion of AAAs are asymptomatic until the development of rupture. AAA rupture is acute and life-threatening.

AAA is a prevalent and highly-fatal disease. In the United States and European countries, it is estimated that AAAs affect 1% to 2% of the general population aged 50 years and above.[1-11] The prevalence of AAA varies by region worldwide. In general, prevalence (among ≥ 25 years) is higher in developed than developing countries.[12] A pooled analysis showed that in 2010 Australasia had the highest prevalence (approximately 0.31%), while the Central Asia had the lowest prevalence (approximately 0.11%).[12] Each year, approximately 200,000 American adults are diagnosed with AAA; of those, 7.5% may have AAAs large enough to be considered high risk for rupture.[13] A rupture, which is often fatal and may occur without symptoms, is the primary cause of AAA mortality. In the United States, acute AAA rupture causes approximately 17,000 deaths each year.[14] Although mortality upon rupture has decreased from 1970s to 2010s, at most 5% to 30% of persons with a ruptured AAA survived, indicating that AAA fatality remains high.[15-17] Since smoking is a well-known strong predictor of AAA, change in AAA mortality may be due to change in cigarette

smoking.[18] Global trends in age-standardized AAA mortality from 1994 to 2010 across 19 countries show substantial heterogeneity.[19] For example, the age-standardized rate of AAA mortality increased in Hungary and Romania while it decreased in the U.S. and United Kingdom for both males and females.[19] Therefore, AAA constitutes an important public health issue both in the U.S. and globally.

1.2 Asymptomatic AAAs and elevated aortic diameters represent highly risky status

Considering the fast expansion rate of AAA (the estimated mean growth rate: 0.13 to 0.57 cm per year), an asymptomatic AAA will have a high likelihood of becoming large within a few years and potentially rupture.[20-23] Over the last 30 year period before 2000, AAA incidence has substantially increased in the US and in the European countries; concurrently AAA mortality has slightly declined but still remains at a high level.[18,24-26] Considering the large proportion of people with AAAs that are asymptomatic until the development of acute and life-threatening rupture, examining risk factors for asymptomatic AAAs in the normal range is a public health priority for AAA prevention.

Although there is no consensus for defining AAA,[16,27] most studies defined an AAA as an infrarenal aortic diameter (IAD) of 3.0 cm and larger.[16,28-37] However, the threshold of IAD for defining an abdominal aortic aneurysm is somewhat arbitrary. The 3 cm cutpoint was chosen because it is more than two standard deviations (2.0 - 2.1 cm) above the average maximum IAD in the

general population,[38] but abdominal aortic diameters vary somewhat by age, sex, and body size.[39,40] Autopsy studies have shown that patients with IAD < 3 cm still have ruptures.[41,42] Some organizations have advocated the use of other definitions. For example, the Society for Vascular Surgery and the International Society for Cardiovascular Surgery recommended that AAA be defined as an IAD 50% greater than the population means reported in the literature.[43] Therefore, investigation of IADs under 3 cm, particularly IADs 2.2 - 3 cm, might still be of potential value to identify people at high risk of AAA or other disease.

Several prospective cohort studies have examined the risk of future AAA and other cardiovascular events for those people with IAD under 3 cm. Freiberg et al reported an IAD 2 - 3 cm vs. an IAD < 2 cm had 1.14 (95% CI: 1.02, 1.27) times risk of future cardiovascular events, with adjustment for age, race, renal insufficiency, smoking status, pack-years of smoking, height, weight, hypertension, diabetes, and LDL and HDL cholesterol, subclinical and clinical cardiovascular disease status.[36] Furthermore, data from the Tromso study in Europe and an Australian cohort showed that compared to an IAD 2.1 - 2.3 cm, IADs 2.4 - 2.6 cm and 2.7 - 2.9 cm were associated with 2.4 and 4.2 times risk of future AAA, 1.2 and 1.3 times of all-cause mortality, 1.2 and 1.8 times of cardiovascular disease mortality.[44-46] The results also showed that people with IAD < 2.0 cm did not have lower risk of future AAA and cardiovascular events than people with IAD 2.1 - 2.3 cm.

In summary, an elevated IAD, or an IAD above 2.1 - 2.3 cm, appears associated, albeit not linearly, with increased risk of AAA, CVD mortality, or all-cause mortality. Therefore, an elevated IAD under 3 cm (particularly 2.3 – 3.0 cm) may indicate a pre-AAA stage, carrying increased risk for AAA and cardiovascular events.

1.3 Determinants of AAA

Given the high prevalence of AAA in the elderly and high fatality of AAA rupture, primary prevention of AAA deserves high priority for public health. The investigation with the aims of examining the determinants of AAA occurrence is needed and has potential of improving strategies for primary prevention. Summary of cardiovascular risk factors in relation to symptomatic AAA from prospective cohort studies is shown in **Table 1.1**.

1.3.1 AAA shares several determinants with atherosclerosis

Prospective cohort studies have suggested that smoking, hypertension, dyslipidemias, advanced age, male gender, and novel atherosclerosis risk factors including increased levels of D-dimer, fibrinogen, C-reactive protein, N-terminal pro-brain natriuretic peptide, and troponin T, are associated with higher risk of AAA.[1,47-52] These factors are also traditional risk factors for atherosclerosis disease. Interestingly, diabetes which is another established risk factor for atherosclerosis, has been associated with lower risk of AAA.[53]

It is unclear whether atherosclerosis itself is a risk factor for AAA. The most recently released guideline by the U.S. Preventive Service Task Force stated that atherosclerosis was a risk factor for AAA; however, literature reviews included in this guideline and supporting this conclusion were from a cross-sectional survey.[16,54] To date, data on this topic from population-based cohort studies is still sparse. Data from the Tromso study has examined the relation between subclinical markers of atherosclerosis and AAA, by relating baseline carotid plaques and plaque growth with change in abdominal aortic diameter over 6 years.[55] That study reported that a one-standard-deviation increase in carotid plaque area was associated with 0.12 mm growth in IADs. However, that study had a limited number of AAA cases (N = 130).[55] More studies are needed to further examine this issue.

1.3.2 Negative association between diabetes and AAA

The relation between diabetes and AAA has been examined in cross-sectional studies, case-control studies and prospective cohort studies.

A meta-analysis of 14 cross-sectional studies examined the possible relation between diabetes and prevalent AAA.[56] This meta-analysis did not find a significant association between diabetes and prevalent AAA.[56] Since the 2004 meta-analysis only included cross-sectional studies, it was subject to potential limitations such as influence of reverse causality.

Recent large case-control studies and prospective cohort studies have reported inconsistent associations between diabetes and AAA in various populations; some studies showed an inverse relationship,[48,52,57-61] while others did not show an association.[38,49,62-68] (**Tables 1.2 and 1.3**) A meta-analysis in 2015 which pooled data from case-control and prospective cohort studies reported a negative association between diabetes and AAA.[69] However, that meta-analysis only included small number of studies (two case-control studies and six cohort studies), could not assess the effects of potential confounders (three cohorts without adjustment for age, sex, race, and smoking), and could not study the subgroups (e.g., population-based/ clinical-based groups) due to limited number of included studies.

Genetic epidemiologic studies may provide additional information on the possible relationship between diabetes and AAAs. A Mendelian Randomization study conducted in Dutch descents did not show an association between AAA and the instrumental variable which was defined based on genotypes of 65 single-nucleotide polymorphisms associated with type-2 diabetes.[70] That evidence suggested that type-2 diabetes was not associated with AAA.[70] Another Mendelian randomization study reported that genetic variants that lead to inhibition of Interleukin-1 are associated with AAAs but not with diabetes.[71] In contrast, randomized controlled trials showed that anakinra, an interleukin-1 receptor antoganist, decreased HbA1c levels.[72-74] Dyslipidemia is a hypothesized risk factor for diabetes. A genome-wide association study showed that rs1466535,

located within intron 1 of low-density-lipoprotein receptor-related protein 1, is significantly associated with AAAs.[76] However, Mendelian randomization study results should be interpreted with caution because of the possible limitations related to the assumptions of Mendelian randomization analysis such as potential pleiotropic effect, weak instruments, etc.[75] Therefore, evidence from genetic studies did not consistently support inverse relationship between diabetes and AAAs.

Therefore, the relationship between diabetes and AAA has been inconsistent across published studies. Additional well-designed studies with large sample sizes are needed to examine the association between diabetes and AAA and the associations by subgroups.

1.3.3 Determinants of asymptomatic AAA and aortic size

Little is known about the determinants of asymptomatic AAAs, though risk factors for symptomatic AAAs have been studied.[1,47-52] Prospective cohort studies have suggested that male sex, white race, greater height, smoking and dyslipidemia are risk factors for asymptomatic AAA detected by ultrasound exam.[47,50,52] Most of these variables are also risk factors for atherosclerosis, but no study has examined the relation between atherosclerosis and asymptomatic AAAs.

Determinants of an elevated IAD among non-AAAs are not established. A few cross-sectional studies conducted in clinical settings have examined this issue, and they reported that greater height and measures of adiposity, male sex, and smoking were risk factors.[77-80] Those risk factors have also been reported in a few population-based cross-sectional studies.[55,81,82] The relation between cholesterol and elevated IAD has only been examined in a sex-specific, age-adjusted univariate analysis.[81] Advanced age was associated with elevated IADs in previous studies conducted in clinic settings[77,78] or in middle-age populations.[55,82] Other population-based studies showed that the median IAD remained stable after 55 years of age;[46,83-85] however, they did not exclude AAAs. Thus, the age-IAD relation is unclear, particularly in elderly populations which are at higher AAA risk than middle ages. Some studies have reported being free of diabetes is a risk factor,[55,78] but newly-diagnosed diabetes was not related to elevated IAD in one study.[77] It is unclear whether duration of diabetes matters in

the diabetes-IAD relationship. To our knowledge, most previous population-based studies of IADs also included AAAs that were likely symptomatic; and most studies did not conduct a separate analysis of elevated IAD among participants without AAA.[55,81] Some studies reported association estimates that were not adjusted for some essential confounders such as lipids and smoking.[82] Therefore, more well-designed, population-based studies conducted among patients free of AAA are warranted.

Major determinants for atherosclerotic CVD, clinical AAA occurrence, ultrasound-detected AAA occurrence, and elevated IAD among non-AAAs are summarized in **Table 1.4.**

1.4 AAA pathophysiology

It is well-known that AAAs are characterized by destruction of aortic walls, but a complex pathophysiology is involved in the process (**Figure 1.1**). Several pathways have been identified to be involved in the formation of an AAA: upregulation of metal matrix metalloproteinases (MMPs) and other proteinases, activation of chronic aortic wall inflammation; and infiltration of mononuclear phagocytes and antigen-driven T cells.[86,87] MMPs and other proteinases are very important in the formation of an AAA, and other risk factors likely act through MMPs and proteinases pathways.[86,87] It is worth noting that a number of proteins relevant to the arterial wall and pro-inflammatory cytokines appear to be involved.[88-90] Smoking may stimulate some endogenous products such as oxidized lipoproteins, localized tissue hypoxia, cytokines, chemokines, and

elevated local expression of angiotension, all of which have been linked to pathways of inflammation and immune system.[91] Moreover, AAA can be formed after Marfan's syndrome and some infectious diseases such as Chlamydia pneumoniae infection and syphilis.[92] The underlying mechanisms are unclear.

Atherosclerosis is widespread throughout the vasculature while AAA occurs only in some specific locations. Although atherosclerosis initially occurs in the intima, it promotes the dilation or shrinkage of the tunica media and adventitia, which in turn produces collagen and elastin fragments and promotes vascular remodeling via a disturbance in the synthesis and degradation of matrix proteins.[93,94] Regarding the potential pathway from atherosclerosis to AAA, angiotensin-2, endothelin-1, and oxidative stress, which are involved in the development of atherosclerotic diseases, have been associated with increased risk of AAA.[95-97] Data from early animal studies showed that the expansion of atherosclerotic plaques which include matrix fibers may simultaneously dilate and weaken aortic walls that support mural tension and then lead to aneurysmal enlargement.[98] That evidence indicates that aneurysms often form after prolonged exposure to atherogenic conditions. In addition, atherosclerotic lipid plaques may be associated with later expansive remodeling of the vessel and arterial dilation.[99]

Proteolysis and matrix destruction, including accelerated collagen turnover and elastin depletion, are mechanisms involved in the pathophysiology of AAA, which result in progressive dysfunction of aortic elastin and collagen in the walls,

increasing the risk of AAA.[100,101] Diabetes is characterized by increased matrix volume which thickens the basement membrane and in turn may reduce the risk of AAAs.[102] Diabetes has been associated with an increase in connective tissue and a decrease in aortic wall stress, while AAA formation is associated with increased aortic wall stress.[103,104] On the other hand, the manifestations of AAA and diabetes have some physiological features in common. For example, both increase arterial stiffness,[104,105] and stimulate transforming growth factor - β1 expression which is a secreted protein that performs cell proliferation and apoptosis.[106,107] In summary, although paradoxical differences in pathophysiology between AAAs and diabetes have been suggested, literature in general suggest that diabetes may increase matrix volume which thickens the basement membrane and avoids progressive dysfunction of aortic elastin and collagen in the walls.[102]

Genetic variants may contribute to the formation of AAA. Family history is a known risk factor for development of an AAA. It is estimated that approximately 15% of patients with an AAA have a positive family history. Genetic linkage analysis of families with AAAs has identified two loci on chromosomes 19q13 and 4q31 that correlate with a susceptibility to the formation of AAA when sex and family history are taken into account.[108] Although candidate genes in these two regions may be linked to the formation of AAA, to our knowledge, no single genetic polymorphism in that area has been identified as a determinant of AAA. Nonetheless, a meta-analysis of 13 studies including 1,258 cases and 1,406

controls showed that MMP-3 rs3025058, a common single nucleotide polymorphism (SNP) within the MMP-3 promoter region, is associated with higher risk for AAAs.[109] An exome sequencing for AAA confirmed 34 protein-altering somatic mutations in 25 genes which may contribute to the development of AAA.[110] Moreover, genetic variants may be involved in many other process involved in the pathophysiology.

1.5 Tables

Table 1.1 Summary of cardiovascular risk factors in relation to symptomatic AAA from prospective cohort studies

Groups	Individual factors	Association	Ref
Cohort studies			
Demographics	Age	++	47-50,52,111
	Male sex	++	
	White race	+	
Lifestyle	Cigarette smoking	+++	47-50,64,111
Anthropometric	Body height	+	47,48,50,52,111
	Weight	?	
Metabolic risk factors	Hypertension	+	47-50,63,64,111

	Total cholesterol	+	
	Low-density lipoprotein cholesterol	+	
	High-density lipoprotein cholesterol	-	
	Diabetes	-	
Circulating biomarkers	White blood cell (WBC)	+	[51]
	Fibrinogen	+	
	C-reactive protein (CRP)	+	
	N-terminal pro-brain natriuretic peptide (proBNP)	+	
	D-dimer	+	
	Tropinin T	+	
Cross-sectional studies or case-control studies			
Lipid lowering medication	Statin use	-	[5,112]

Subclinical indices by ultrasound	Carotid intima-media thickness (cIMT)	+	[55,113]
	Carotid atherosclerotic plaque	+	
Family history	Family history of AAA	++	[16]
Circulating biomarkers	matrix metalloproteinase (MMP)-3	+	[86,114]
	MMP-9	+	
	N-terminal propeptide of Type Ill procollagen (PIIINP)	+	
	Interleukin (IL)-6, IL-1beta		
	Osteopontin	+	
		+	

Table 1.2 Characteristics of included studies examining the association between diabetes and AAA

Author	Year	Setting	Design	Follow-up year	N total	N case	DM definition	AAA ascertainment	AAA definition
Baumgartner	2008	clinical	cohort	1	68236	1752	DM treatment record	clinical records	Not provided
Blanchard	2000	clinical	case-control	N/A	200	98	FG ≥7 mmol/L or self-reported DM diagnosis or DM treatment	ultrasound scan	Any definite focal widening classified as AAA, 92% ≥3 cm
Franks	1996	clinical	case-control	N/A	288	44	self-reported DM diagnosis	clinical records	Not provided
Iribarren	2007	population	cohort	13	104813	605	self-reported DM diagnosis	clinical records	ICD-9:441.3, 441.4
Jahangir	2015	population	cohort	4.9	18782	281	self-reported DM diagnosis	clinical records	ICD-9:441.3, 441.4
Lederle	2008	population	cohort	7.8	161808	184	self-reported DM	clinical records	Not provided

							diagnosis		
Ohrlander	2012	population	cohort	13	246957	3335	DM treatment record	clinical records	ICD-10: I71.3, I71.4
Robin	2003	population	cohort	30	19274	418	self-reported DM diagnosis	clinical records	ICD-9: 441.3, 441.4, ICD-10: 71.3, 71.4
Shah	2015	population	cohort	5.5	1921260	3051	DM treatment record	clinical records	Not provided
Smelser	2014	clinical	case-control	N/A	11411	888	type-2 DM related death and hospital discharge records	Clinical records and ultrasound scan	ICD-9: 441.3, 441.4 Max IAD ≥3 cm
Tang	2016	population	Cohort	22.5	15703	588	FG ≥7 mmol/L or Non-FG ≥11.1 mmol/L, self-reported DM diagnosis and treatment	clinical records	ICD-9: 441.3, 441.4 ICD-10: 71.3, 71.4 Procedure code 38.44, 39.71

Tornwall	2001	population	cohort	5.8	29133	181	self-reported DM diagnosis	clinical records	ICD-8:441.00-441.99 ICD-9: 441.0A-441.9x Procedure code: 39.71
Wanhainen	2005	population	case-control	N/A	175	35	self-reported DM diagnosis	ultrasound and computed tomography scan	Mean max IAD by the two methods ≥3 cm
Wong	2007	population	cohort	4	39352	376	self-reported DM diagnosis	clinical records	Not provided
Stackelberg	2017	population	cohort	13	14249	168	self-reported DM diagnosis	ultrasound scan or self-reported treatment	Max IAD ≥3 cm
Wang	2017	population	cohort	10.4	25554	471	self-reported DM diagnosis	Self-reported diagnoses,	ICD-9: 441.3, 441.4

			clinical records

Table 1.2 Characteristics of included studies examining the association between diabetes and AAA (cont')

Author	Year	Relative Risk (95% confidence interval)	Covariates
Baumgartner	2008	0.59 (0.53, 0.66)	age, sex, race, smoking, HTN, and dyslipidemia
Blanchard	2000	0.32 (0.12, 0.87)	age, sex, smoking, and family history
Franks	1996	0.33 (0.04, 2.67)	age and sex matched
Iribarren	2007	0.62 (0.37. 1.05)	age, sex, race, education, height, weight, smoking, alcohol, white blood cell counts, chronic kidney disease, HTN, CVD, and hormone use.
Jahangir	2015	0.75 (0.54, 1.05)	sex, race, education, BMI, smoking, CVD, and HTN
Lederle	2008	0.29 (0.13, 0.66)	age, sex, race, height, weight, smoking, alcohol, CVD, HTN, COPD, hormone use, and lipid meds

Ohrlander	2012	0.40 (0.21, 0.76)	age, income, HTN, CVD and COPD
Robin	2003	0.80 (0.43, 1.51)	N/A
Shah	2015	0.46 (0.35, 0.60)	age, sex, deprivation, BMI, smoking, lipids and lipid meds, BP and BP meds
Smelser	2014	0.43 (0.29, 0.64)	age and sex matched
Tang	2016	0.52 (0.36, 0.75)	age, sex, race, height, smoking, alcohol, lipids, HTN and PAD
Tornwall	2001	0.43 (0.16, 1.15)	age, education, BMI, smoking, physical activity, BP, lipids, and trial group
Wanhainen	2005	0.75 (0.11, 5.12)	N/A
Wong	2007	0.55 (0.26, 1.17)	age, smoking, BMI, physical activity, HTN and dyslipidemia,
Stackelberg	2017	0.52 (0.25, 1.09)	education, smoking, BMI, WC, diet, physical activity, alcohol intake, HTN, CVD, and dyslipidemias
Wang	2017	0.58 (0.51, 0.66)	age, race, trial assignment, BMI, smoking status, alcohol use, physical activity, and history of HTN, CVD dyslipidemias

AAA, abdominal aortic aneurysm; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes; FG, fasting glucose; IAD, infrarenal aortic diameter; HTN, hypertension; NDI, National Death Index; PAD, peripheral artery disease.

Table 1.3 Baseline characteristics of populations in the studies examining diabetes in relation to abdominal aortic aneurysm.

Author	Mean age, year	Male	White	Mean height, cm	Current smoking	Prevalent HTN	Prevalent diabetes	Comorbidities
Baumgartner	68.6 (10.1)	63.0%	67.2%	N/A	14.8%	81.8%	44.0%	With established CVD, or with ≥3 CVD risk factors
Blanchard	69.0	51.0%	100.0%	N/A	26.9%	38.4%	14.5%	Not indicated
Franks	70.4 (10.5)	83.0%	100.0%	172	100.0%	20.7%	6.3%	Not indicated
Iribarren	43.9 (14.1)	44.8%	82.0%	167	37.3%	36.5%	3.2%	Not indicated
Jahangir	64.4 (5.6)	63.9%	40.0%	168	21.2%	71.3%	30.0%	Not indicated
Lederle	63.2 (7.2)	0.0%	82.5%	162	6.9%	38.9%	5.9%	Not indicated
Ohrlander	71.4	43.4%	100%	N/A	N/A	N/A	2.4%	Not indicated
Robin	50.5 (6.6)	54.9%	94.9%	169	38.0%	59.1%	3.4%	Not indicated

Shah	46.9 (14)	49.4%	90.0%	N/A	20.5%	N/A	1.8% [b]	Not indicated
Smelser	N/A	42.2%	100.0%	N/A	N/A	N/A	N/A [b]	Not indicated
Tang	54.2 (5.8)	44.8%	72.9%	169	26.1%	35.0%	11.9%	Not indicated
Tornwall	57 (53-61) [a]	100.0%	100.0%	N/A	100.0%	N/A	4.0% [a]	Not indicated
Wanhainen	N/A	83.0%	100.0%	N/A	12.0%	43.2%	11.4%	Not indicated
Wong	53.3	100.0%	N/A	N/A	9.6%	19.3%	2.0%	Not indicated
Stackelberg	55.3 (4.2)	100%	100%	N/A	22.3%	17.9%	4.6%	Not indicated
Wang	65.5 (8.3)	100%	90.50%	N/A	3.8%	45.9%	7.6%	Not indicated

CVD, cardiovascular disease; HTN, hypertension.

[a] Median value (Interquartile range).

[b] Type-2 diabetes only.

Table 1.4 Summary of determinants for atherosclerotic CVD, abdominal aortic aneurysm (AAA) occurrence and elevated infrarenal aortic diameter (IAD) among people without AAAs.

Determinants	Atherosclerotic CVD	Clinical AAA occurrence	Ultrasound-detected AAA occurrence	Elevated IAD among non-AAAs
Age	++	+	?	+
White race (vs. black)	-	+	+	-
Male sex	+	+++	++	++
Height	-	+	+	+
Obesity	+	+	+	+

Smoking	++	+++	++	?
Diabetes	+	-	?	?
Hypertension	++	+	?	?
Dyslipidemia	+	+	+	?

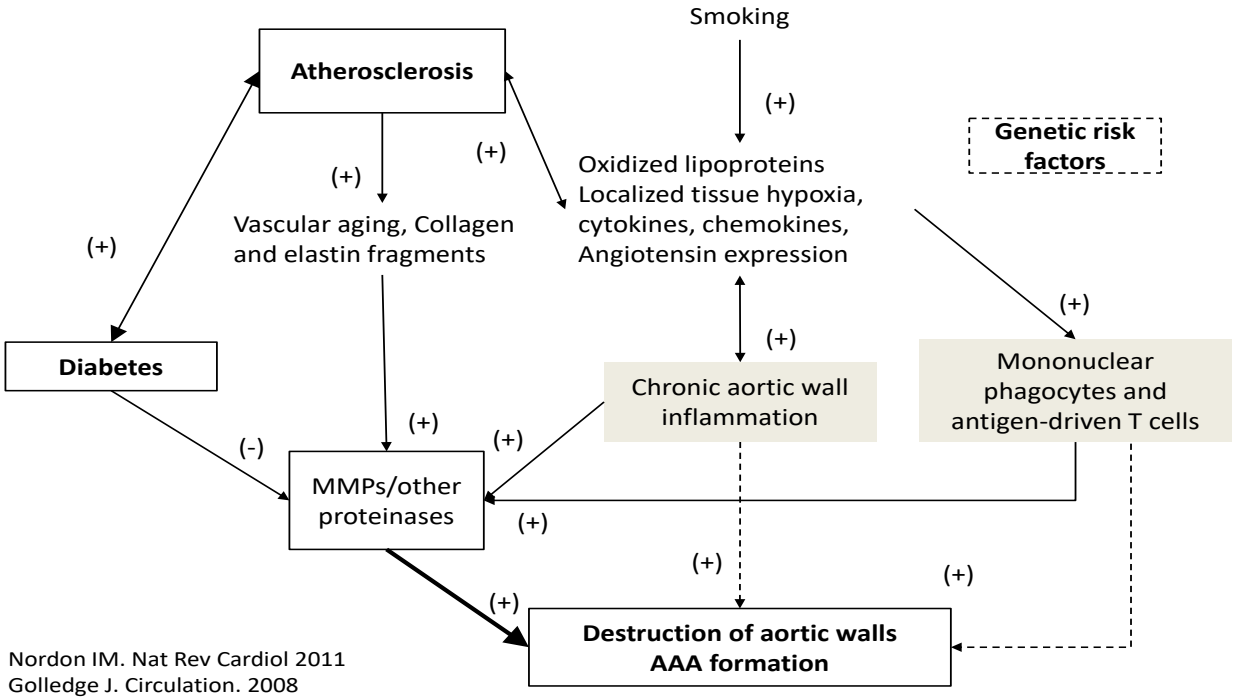
+, possible risk factor;

-, possible protective factor;

?, unclear.

1.6 Figures

Figure 1.1 Pathophysiology of AAA



Chapter 2. Detailed Methods

2.1 The ARIC Study: Design and Population

The ARIC study was designed to investigate risk factors for atherosclerosis and its clinical sequelae.[115] The ARIC investigators created a cohort comprising 15,792 biracial men and women aged 45 - 64 from four communities (Washington County, MD; Forsyth County, NC; Jackson, MS; and suburban Minneapolis, MN) in 1987-89. The ARIC conducted follow-up examinations in 1990-92 (Visit 2), 1993-95 (Visit 3), 1996-98 (Visit 4), 2011-13 (Visit 5), and 2016-17 (Visit 6). The seventh visit is ongoing. ARIC administered a telephone interview annually or semiannually through 2014 to ask about any interim hospitalizations or deaths and these records were sought to identify cardiovascular events including AAAs. To identify additional hospitalizations or deaths, the ARIC study also conducted surveillance of local hospital discharge lists for cohort members. For each hospitalization identified through 2014, all International Classification of Disease (ICD)-9-CM discharge codes were recorded. Additionally, ARIC linked participant identifiers with Medicare data from the Centers for Medicare and Medicaid Services (CMS) for 1991-2011, to find any missing hospital or outpatient events for those over 65 years.

2.2 Data Collection in ARIC

2.2.1 Clinical AAA ascertainment

Although participants were not queried about AAA history at the baseline examination (ARIC Visit 1) in 1987-89, they were asked extensively about prior arterial surgery. Clinical AAAs were identified by searching hospitalization, death records, and Medicare data. ARIC obtained any interim hospitalizations and identified deaths by conducting annual telephone calls with participants. ARIC also identified additional hospitalizations or deaths by conducting surveillance of local hospitals. Participants' identifiers were linked to Medicare data from the Centers for Medicare and Medicaid Services (CMS) for 1991-2011, which was used to find additional hospital or outpatient events for those over 65 years. Clinical AAAs were defined as participants who had a hospital discharge diagnosis from any of the above sources, or two Medicare outpatient claims that occurred at least one week apart with ICD-9-CM codes of 441.3 (ruptured AAA) or 441.4 (AAA without mention of rupture), or procedure codes of 38.44 (AAA resection and replacement) or 39.71 (AAA endovascular repair), or a listed cause of death coded as ICD-9 code 441.3 or 441.4 or ICD-10 code I71.3 (ruptured AAA) or I71.4 (AAA without mention of rupture).[52] AAA based on procedure codes were required to be verified by diagnosis codes. Both symptomatic and asymptomatic AAAs were medically documented. Thoracic, thoracoabdominal, or unspecified aortic aneurysms were not deemed as clinical AAA events but treated as non-events in this study (**Tables 2.1 - 2.2**).

2.2.2 Asymptomatic AAA and abdominal aortic size by ultrasound

In the fifth ARIC examination (2011-13), a screening abdominal ultrasound was performed among 5,913 participants (59% of the 10,036 surviving ARIC participants through August 2013) to measure abdominal aortic diameters to identify additional asymptomatic AAAs in the surviving ARIC cohort.

Both a radiologist and an ultrasound technician specializing in vascular imaging centrally trained experienced cardiac ultrasonographers from each ARIC field center in the technique of abdominal aortic scanning. Certified site sonographers followed standard protocols and obtained images with a Philips iE33 high resolution duplex scanner using a Philips C5-1 transducer and read all images in the field centers. Certified sonographers measured the following points of the aorta directly across the largest anterior posterior (AP) (front to back) or transverse (side to side) diameter to the outer edge of the wall on the opposite side: at the proximal aorta just below the superior mesenteric artery, the proximal infrarenal aorta 2 cm below the renal arteries, the distal infrarenal aorta 1 cm above the bifurcation, and the point of maximal infrarenal aortic diameter (IAD). A longitudinal view of the infrarenal aorta was also recorded to demonstrate whether the aneurysm begins above, at, or below the renal arteries. A maximum IAD was used to represent the size of AAAs and to define asymptomatic AAA. An asymptomatic AAA was defined by a maximum IAD ≥ 3 cm, as commonly used in the literature.[16,28-36,82] To ensure the completeness of identification of asymptomatic AAAs, experienced physicians specializing in

vascular imaging over-read any image that the sonographers recorded had > 2.8 cm IAD or any possible vascular or non-vascular pathology, plus a 5% of the remaining cohort.

Ultrasonography is accepted as the standard method of screening imaging for AAA due to several advantages. Ultrasonography is a low-cost and noninvasive method, and does not involve radiation exposure. It has a high sensitivity (≥ 94%) and specificity (≥ 98%).[116-121] Although a computed tomography scan is also highly sensitive and specific in detecting AAAs, it is not recommended for first-line screening and therefore not useful in an epidemiological study, because of high cost and radiation exposure.[16,116,122]

2.2.3 Carotid artery ultrasound measures

At Visits 1 to 4, ARIC measured cIMT bilaterally in the extracranial carotid arteries, namely in the common carotid artery (1 cm proximal to the dilatation of the carotid bulb), the carotid bifurcation (1 cm proximal to the flow divider), and the internal carotid artery (1 cm distal to the flow divider). The mean cIMT was produced by combining the averages of cIMT measures at the six carotid sites. A previous study has reported that between-reader reliability coefficients ranged from 0.78 to 0.93 and coefficients of variation ranged from 13.1% to 18.3% in ARIC Visit 1.[123] The presence of atherosclerotic plaque at any of the 6 segments was recorded by ARIC ultrasound readers as wall thickness in excess of 1.5 mm or the presence of lumen encroachment or irregular intimal surface and/or image characteristics indicative of structural heterogeneity of the arterial wall.

In the carotid ultrasound examination at Visit 2, the diastolic arterial diameter and the arterial diameter change, which represents change in arterial diameter between systole and diastole from the left carotid artery during cardiac cycles, were measured. Change in arterial diameter is an index of arterial stiffness. Concurrent brachial blood pressure was measured every 5 minutes with an automated oscillometric device (1846SX Dinamap), and the mean of the two blood pressure measures before the completion of ultrasound examination was used in calculating arterial stiffness indices. Pulse pressure was defined as the difference between systolic and diastolic blood pressure. Based on these ultrasound and blood pressure measures, several indices of stress-strain ratio were generated to represent carotid artery distensibility, including Peterson's elastic modulus, Young's elastic modulus, and beta index. Specifically, Peterson's elastic modulus was calculated as (pulse pressure * diastolic arterial diameter)/ arterial diameter change; Young's elastic modulus was calculated as [Petersons' elastic modulus * diastolic arterial diameter / 2 * cIMT]; and beta index was calculated as log (systolic blood pressure / diastolic blood pressure) / (arterial diameter change / diastolic arterial diameter). More details on the measurement of these indices have been reported in previous studies.[124,125]

2.2.4 Demographic and lifestyle variables

In home interview and clinical examination at Visits 1 to 5, standardized questionnaires were used to obtain demographic information, educational status, lifestyle factors, medication use, and history of disease. Smoking status and

history were assessed by self-report. Smoking status was categorized as never, former (more than 100 cigarettes in the past), or current at each Visit.[126] Smoking pack-years were calculated among the current and former smoker groups, based on the number of cigarettes per day and duration of smoking. Alcohol consumption was self-reported at all Visits. Usual alcohol consumption (in grams per week) was calculated based on the frequency of consumption of wine, beer and liquor, assuming that 4 oz of wine contains 10.8 g, 12 oz of beer contains 13.2 g, and 1.5 oz of liquor contains 15.1 g of ethanol. Physical activity was assessed by interview using a questionnaire developed by Baecke in Visits 1 and 3.[127,128] The questionnaire included 16 items about usual exertion, and three indexes ranging from 1 (low) to 5 (high) were derived for physical activity at work, during leisure time, and in sports. Leisure time physical activity showed no relation with carotid atherosclerosis, so associations are shown for the work and sport indexes only.

2.2.5 Diabetes, serum glucose, and hemoglobin A1c

In ARIC, participants were asked to fast for 12 hours before each examination. Blood specimens were collected into vacuum tubes, then centrifuged at 3000g for 10 minutes at 4°C, and then stored at -70°C until analysis within a few weeks. In Visits 1 and 2, serum glucose was assessed by the hexokinase method. In Visits 3, 4 and 5 serum or plasma glucose (Visit 3 only included plasma glucose) was measured using glucose-6-phosphate dehydrogenase method. Reliability coefficient for serum glucose was 0.84 in

participants examined several times,[129] and quality control data for the other exams was similar. Prevalent diabetes mellitus was defined as a fasting glucose > 126 mg/dL, a nonfasting glucose > 200 mg/dL, and/or a history of or treatment for diabetes.

Hemoglobin A1c was measured on 4918 participants in 2003-2004 using the Tosoh 2.2 Plus HPLC instrument (Tosoh Bioscience, South San Francisco, CA, USA), and on the remaining 9151 participants using the Tosoh G7 HPLC instrument in 2007-2008.[130] In a validation study, the coefficients of variation were 1.8% (N = 89) in 2003-2004 and 1.4% (N = 259) in 2007-2008.[131] The correlation between measurements at the two time points was high (r = 0.99).

2.2.6 Lipids

Plasma lipids were measured in each ARIC Visit. Plasma total cholesterol and triglycerides were measured by enzymatic methods, and LDL cholesterol was calculated using Friedewald methods (plasma triglyceride levels ≤ 400 mg/dL).[132,133] If plasma triglycerides levels were > 400 mg/dL, LDL cholesterol was not calculated. HDL cholesterol was measured after dextran-magnesium precipitation.[134] The lipid laboratory participated in the Centers for Disease Control Standardization Program throughout the study. As demonstrated in an intra-individual variability study, reliability coefficients (r) were ≥ 0.85 for LDL-C, HDL-C, and triglycerides in ARIC Visit 1.[135] Quality control data for lipids measured in other visits are similar.

2.2.7 Blood pressure and hypertension

In clinic examinations, after a 5-minute rest period, repeated blood pressures were obtained in seated participants by certified technicians using random zero sphygmomanometers. At Visits 1, 2, and 3, systolic and diastolic fifth phase blood pressures were measured three times in the right arm of seated participants. The mean of the last two measurements was used in analysis. At Visits 4 and 5, seated blood pressure was measured twice, and then averaged.

Prevalent hypertension was defined as systolic pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg or use of antihypertensive medications.

2.2.8 Anthropometric measurements

At each ARIC Visit, weight was measured in standard scrub attire without shoes using a scale that was zeroed daily and calibrated quarterly. Height was measured to the nearest centimeter in Visits 1, 3, 4 and 5. Body mass index (kg/m^2) was computed from height and weight. Waist circumference was measured at umbilicus level.

2.2.9 Circulating biomarkers

At Visit 1, white blood cells (WBC) were counted with Coulter counters in each study community. Fibrinogen was measured by the thrombin-time titration method with reagents and calibration materials (Fibriquik) obtained from General Diagnostics (Organon-Technika Co) at Visit 1.[136] At Visit 3, ARIC measured D-dimer concentrations via an immunoturbidimetric assay (Liatest D-DI,

Diagnostica Stago, Parsippany, NJ) on the Evolution analyzer (Diagnostica Stago, Parsippany, NJ). At Visit 4, ARIC measured cardiac troponin T using Cobas e411 analyzer (the Elecsys Troponin T immunoassay, Roche Diagnostics, Indianapolis, IN), N-terminal pro-brain natriuretic peptide (proBNP) using Cobas e411 analyzer (the Elecys proBNP II immunoassay, Roche Diagnostics, Indianapolis, IN), and high-sensitivity C-reactive protein (CRP) by the immunoturbidimetric CRP-Latex (II) high-sensitivity assay using a Hitachi 911 analyzer (Roche Diagnostics, Denka Seiken, Tokyo, Japan). Although intra-individual reliability coefficients were not available for these biomarkers in the ARIC, the reliability coefficient for blinded replicate measurements on split specimens was 0.99 for CRP, 0.99 for proBNP, 0.98 for Tropinin T, 0.92 for D dimer, and 0.72 for fibrinogen.[137]

2.3 Tables

Table 2.1 The 9th and 10th revision of the International Statistical Classification of Diseases (ICD) for aorta aneurysm

	Abdominal aortic aneurysm	**Thoracoabdominal aortic aneurysm**	**Thoracic aortic aneurysm**	**Non-specific sites of aortic aneurysm**
AAA cases (Diagnosis code ICD-9)	441.3: Abdominal aneurysm, ruptured 441.4: Abdominal aneurysm w/o mention of rupture	441.6: Thoracoabdominal aortic aneurysm, ruptured 441.7: Thoracoabdominal aneurysm, w/o mention of rupture 441.03:	441.01: Dissection of aorta, thoracic 441.1: Thoracic aortic aneurysm, ruptured 441.2: Thoracic aortic aneurysm, w/o	441.0: Dissection of aorta 441.00: Dissection of unspecified site of aorta 441.5: Aortic aneurysm of unspecified site, ruptured 441.9:

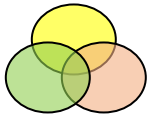
		Dissection of aorta, thoracoabdominal	rupture	Aortic aneurysm of unspecified site w/o mention of rupture
AAA repairs (procedure code ICD-9)	38.44: Resection of vessel with replacement, aorta, abdominal 39.71: Endovascular implantation of graft in abdominal aorta			39.52: Other repair of aneurysm; 38.64: Other excision of vessels, aorta, abdominal
AAA deaths (ICD-9 and ICD-10)	I71.3: Abdominal aortic aneurysm, ruptured	I71.03: Dissection of thoracoabdominal aorta	I71.01: Dissection of thoracic aorta	I71.0: Dissection of aorta I71.00:

	I71.4: Abdominal aortic aneurysm, w/o rupture 441.3: Aortic aneurysm, abdominal ruptured 441.4: Aortic aneurysm, abdominal, w/o rupture	I71.5: Thoracoabdominal aortic aneurysm, ruptured I71.6: Thoracoabdominal aortic aneurysm, w/o rupture	I71.1: Thoracic aortic aneurysm, ruptured I71.2: Thoracic aortic aneurysm, w/o rupture	Dissection of unspecified site of aorta I71.8: Aortic aneurysm of unspecified site, ruptured I71.9: Aortic aneurysm of unspecified site, w/o rupture 441: Aortic aneurysm 441.0: Dissection of aorta 441.5: Aortic aneurysm,

	unspecific, ruptured 441.9: Aortic aneurysm, unspecific w/o rupture

Table 2.2 Definition of Definite and Probable Abdominal Aortic Aneurysm

	Definite AAA **(Specific AAA coding)**	**Probable AAA (uncertain AAA status)** **(Non-specific sites of AA coding, and** **1. Not specific AAA coding;** **2. Not thoracic AA coding;** **3. Not thoracoabdominal AA coding)**
Cases 	(441.3 + 441.4)	(441.0 + 441.00 + 441.5 + 441.9) - (441.3 + 441.4) - (441.01 + 441.1 + 441.2) - (441.6 + 441.7 + 441.03)
Repairs 	(38.44 + 39.71)	(39.52 + 38.64) - (38.44 + 39.71) - (N/A) - (N/A)

Deaths 	(I71.3 + I71.4 + 441.3 + 441.4)	(I71.0 + I71.00 + I71.8 + I71.9 + 441 + 441.0 + 441.5 + 441.9) - (I71.3 + I71.4 + 441.3 + 441.4) - (I71.01 + I71.1 + I71.2) - (I71.03 + I71.5 + I71.6)
Total	Cases+ Repairs+ Deaths (There might be some overlaps among them) 	

If a person had a thoracic or thoracoabdominal AA diagnosis code and a definite repair code of AAA, we categorized that person as a thoracic or thoracoabdominal AA.

Chapter 3. Manuscript 1: Association of Subclinical Carotid Atherosclerosis and Stiffness with Abdominal Aortic Aneurysm: the Atherosclerosis Risk in Communities (ARIC) Study

3.1 Introduction

Abdominal aortic aneurysms (AAA) affect about 1% to 2% of the general population aged ≥ 50 years in the US.[50,138] According to the most recent estimates, AAA rupture causes about 2,446 deaths annually in the US.[139] Thus, AAA is an important public health concern.

There is a debate about whether atherosclerosis is a cause of AAA.[1] Prospective cohort studies have suggested that traditional risk factors for atherosclerotic disease, including smoking, hypertension, dyslipidemia, advanced age, male gender, and some inflammatory and hemostasis biomarkers, are associated with a higher risk of AAA.[1,47-52] In addition, angiotensin-2, endothelin-1, and measures of oxidative stress, which are involved in the development of atherosclerotic diseases, are associated positively with the risk of AAA.[95-97] In contrast, some risk factors for atherosclerosis, such as type 2 diabetes, may decrease the risk of AAA.[53] Pathologically, atherosclerosis is widespread throughout the vasculature,[140] while aortic aneurysms occur only in specific locations of the body such as the abdominal aorta. Moreover, atherosclerosis primarily forms in the intima while AAA primarily affects the media and adventitia.[140] The most recently released guideline by the US Preventive Service Task Force stated that atherosclerosis was a risk factor for AAA;[16] however,

literature reviews included in this guideline to support the statement were based on cross-sectional data for abdominal diameter among patients free of AAA.[16,82]

Current knowledge gaps regarding the determinants of AAA are due to limited evidence. Epidemiologic data on atherosclerosis and AAA are sparse; only one population-based study, to date, has examined the relation between subclinical markers of atherosclerosis and maximal abdominal aortic diameter.[55] Data on the relation between arterial stiffness and AAA are also limited.[141,142] To better understand the possible relationship of generalized measures of atherosclerosis and arterial stiffness with AAA occurrence, we analyzed data collected from a large population-based cohort study with over 20 years of follow-up. We hypothesized that greater baseline carotid intima-media thickness (cIMT) and carotid plaque, and reduced carotid artery distensibility are associated with higher incidence of AAA.

3.2 Methods

3.2.1 The ARIC Study

The ARIC study was designed to investigate risk factors for atherosclerosis and its clinical sequelae.[115] The ARIC investigators recruited a population-based cohort comprising 15,792 men and women aged 45 - 64 from four communities (Washington County, MD; Forsyth County, NC; Jackson, MS; and suburban Minneapolis, MN) in 1987-89 (Visit 1). ARIC conducted follow-up examinations in 1990-92 (Visit 2), 1993-95 (Visit 3), 1996-98 (Visit 4), and 2011-

13 (Visit 5). ARIC administered a telephone interview annually or semiannually to ask about any interim hospitalizations or deaths and these records were sought to identify cardiovascular events including AAAs. To identify additional hospitalizations or deaths, ARIC also conducted surveillance of local hospital discharge lists for cohort members. For each hospitalization identified, all International Classification of Disease (ICD)-9-CM discharge and procedure codes were recorded, and for deaths, the ICD-9 or ICD-10 codes for the underlying cause were recorded. Additionally, ARIC linked participant identifiers with Medicare data from the Centers for Medicare and Medicaid Services (CMS), since 1991, to find any missing hospital or outpatient events for participants over 65 years.

3.2.2 Ascertainment of AAA

Participants reporting prior AAA surgery or aortic angioplasty at baseline were excluded from all analyses. Clinical AAAs were ascertained since the baseline examination through 2011, defined as either a hospital discharge diagnosis from any sources or two Medicare outpatient claims that occurred at least one week apart, with ICD-9-CM codes of 441.3 (ruptured AAA) or 441.4 (AAA without mention of rupture), or procedure codes of 38.44 (AAA resection and replacement) or 39.71 (AAA endovascular repair), or a listed cause of death coded as ICD-9 441.3 or 441.4, or ICD-10 code I71.3 (ruptured AAA) or I71.4 (AAA without mention of rupture).[52] Both symptomatic and asymptomatic AAAs that were medically documented were included. Thoracic, thoracoabdominal, or

aortic aneurysms at unspecified locations were not deemed to be AAA events in this study.

In the fifth ARIC examination in 2011-13, an abdominal ultrasound was performed among 5,911 participants (excluding those with clinical AAA), comprising 59% of the 10,036 surviving ARIC participants through August 2013. Details on the abdominal ultrasound exam in ARIC can be found elsewhere.[52] In short, certified cardiac ultrasonographers obtained images with a Philips iE33 high resolution duplex scanner using a Philips C5-1 transducer. Transverse images of anterior-posterior and transverse diameters were recorded at the proximal aorta just below the superior mesenteric artery, the proximal infrarenal aorta 2 cm below the renal arteries, the distal infrarenal aorta 1 cm above the bifurcation, and the point of maximal infrarenal aortic diameter. A longitudinal view of the infrarenal aorta was also recorded. Infrarenal abdominal aortic maximum diameter ≥ 3 cm was used to define asymptomatic AAA.[16,28-36,82] To ensure the completeness of identification of asymptomatic AAAs, experienced physicians specializing in vascular imaging over-read any image that the sonographers judged had > 2.8 cm infrarenal diameter or probable pathology, plus a 5% random sample of the normal images.

3.2.3 Risk factor assessment

At Visits 1 and 2, ARIC measured cIMT bilaterally in the extracranial carotid arteries, namely in the common carotid artery (1 cm proximal to the

dilatation of the carotid bulb), the carotid bifurcation (1 cm proximal to the flow divider), and the internal carotid artery (1 cm distal to the flow divider). In each 1-cm section, there were up to 11 measurements (along the far wall) at 1-mm intervals.[143] For each Visit, the mean cIMT was calculated by averaging all measures (far wall) from the six carotid sites (**Figure 3.1**). A previous study reported that in ARIC between-reader reliability coefficients for cIMT ranged from 0.78 to 0.93 and coefficients of variation ranged from 13.1% to 18.3%.[123] ARIC ultrasound readers recorded the presence of atherosclerotic plaque at any of the 6 segments, defined as wall thickness more than 1.5 mm or the presence of lumen encroachment, irregular intimal surface, and/or image characteristics indicative of structural heterogeneity of the arterial wall.

In the carotid ultrasound examination at Visit 2, the carotid arterial systolic and diastolic arterial diameters were measured with an ultrasonic echo-tracking radiofrequency device (Autrec 4881-AWT, Winston-Salem, NC).[125] A diameter change was calculated to represent change in arterial diameter between systole and diastole from the left common carotid artery during cardiac cycles. Concurrently, two brachial blood pressures were measured with an automated oscillometric device (1846SX Dinamap, Critikon, Inc., Tampa, FL), and the mean of the two blood pressure measures was used in calculating arterial stiffness indices. Based on the ultrasound and blood pressure measures, Beta Index was generated as a stress-strain ratio representing carotid artery distensibility[125]. Beta Index was calculated as log (systolic blood pressure / diastolic blood pressure) /

(arterial diameter change / diastolic arterial diameter). A higher Beta Index indicates less carotid distensibility. Beta Index has been used as an index of carotid stiffness in ARIC,[125] and is highly correlated with other indices of carotid artery distensibility measured at ARIC Visit 2 (**Tables 3.1 and 3.2).**

In home interview and clinical examinations at Visits 1 and 2, standardized questionnaires were used to obtain information on demographics, lifestyle risk factors including smoking history, medication use, and medical history. Smoking status was categorized as never, former (more than 100 cigarettes in the past), or current smoker at each Visit.[126] Smoking pack-years were calculated among the current and former smoker groups, based on the number of cigarettes per day and duration of smoking. Height was measured without shoes to the nearest centimeter at Visit 1. Weight was measured in a scrub suit to the nearest pound using a beam balance scale at Visits 1 and 2. Body mass index (BMI) was calculated by dividing weight (in kilograms) from the corresponding Visit by height (in meters) squared from Visit 1. At both Visits, systolic and diastolic fifth phase blood pressures were measured three times after a 5-minute rest in the right arm of seated participants by certified technicians using random zero sphygmomanometers. The mean of the last two measurements was used in analysis. Prevalent hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or use of antihypertensive medications. Blood specimens were collected into vacuum tubes, centrifuged at 3000g for 10 minutes at 4°C, and then stored at - 70°C until analysis within a few

weeks. Serum glucose was assessed by the hexokinase method.[144] Prevalent diabetes mellitus was defined as a fasting glucose ≥ 126 mg/dL, a nonfasting glucose ≥ 200 mg/dL, and/or a history of or treatment for diabetes. Plasma total cholesterol was measured by enzymatic methods.[132] HDL cholesterol was measured after dextran-magnesium precipitation[134]. At Visit 1, white blood cells were counted with Coulter counters,[51] and fibrinogen was measured by the thrombin-time titration method with reagents and calibration materials (Fibriquik) obtained from General Diagnostics (Organon-Technika Co).[136]

3.2.4 Statistical analyses

SAS (Version 9.4, SAS Institute Inc., Cary, NC, USA) was used in all analyses. We included ARIC participants who had carotid ultrasound measures at ARIC Study Visits 1 or 2 (N = 15,671), all of whom were then followed for clinical AAA status. For the analysis of cIMT and plaque, we excluded 55 participants who were in race groups other than white or black or blacks in Minneapolis or Washington County, 11 who had prior AAA surgery, and 30 with uncertain AAA status during follow-up. We further excluded 1,002 participants without measurement of cIMT, leaving a final sample size of 14,573. For the analysis of Beta Index which was measured at Visit 2 only, we excluded from 14,348 participants of baseline population 91 who were in race groups other than white or black or blacks in Minneapolis or Washington County, 22 who had AAA surgery or AAA prior to Visit 2, 24 with uncertain AAA status during follow-up,

and 3,921 without carotid Beta Index, leaving a final sample of 10,290 participants.

Carotid plaque (yes/no) measured at Visit 1 and Beta Index measured at Visit 2 were analyzed. For cIMT analyses, if the measurement was available only at Visit 1, or if a participant had an AAA between Visits 1 and 2, then the Visit 1 measure of cIMT was used. Otherwise, the average cIMT value of both Visits 1 and 2 (three years apart) was used in the analysis to reduce random error in the measurement. In both situations, ARIC Visit 1 was baseline for the analysis of cIMT. Both cIMT and Beta Index were categorized into quartiles in the analysis.

The associations of measures of carotid atherosclerosis and stiffness with AAA were examined separately for clinical and ultrasound-detected AAAs. First, restricted a cubic spline was used to examine the shape of associations between continuous exposure variables (cIMT and Beta Index) and risk of AAA (clinical AAA only due to the relatively small sample size of the ultrasound AAA analysis). Unlike regression-based models, the spline method does not assume the shape of association but can fit complex distribution and linear regression.[145] The shape of association is dependent on polynomials.[146,147] Cubic spline, which is most widely used, includes a linear, a quadratic, and a cubic term to the category-specific models to allow for a slope within category and to avoid a ‘sudden jump’ between categories. Also, if symmetric cutpoints are chosen, which almost always occurs, the shape is related to the number of cutpoints rather than the location of cutpoints.[146] Since the number of cutpoints determines the degree of

smoothing, the more knots, the less smoothing. Typically, a small number of knots (between 3 and 8) are used. In this analysis, we started to use three cutpoints within cubic splines. We also used the restricted form of cubic spline, which excludes those in the upper 1% and the lower 1% of continuous exposure variables so as to provide conservative estimates for the tail regions and thus reduce the influence of outliers.[145] If a linear relationship was found from restricted cubic spline, we used a linear model. If a non-linear relationship was observed, we considered non-linear techniques such as square or log transformations. In a special case where a threshold pattern of association was observed, we considered re-categorizing the data or analyzing it separately by the threshold.

For the clinical AAA analysis, we plotted Kaplan-Meier curves to depict the unadjusted association of cIMT and Beta Index with clinical AAA risk. We used Poisson regression models to generate crude incident rates of AAA, and presented rates by category of exposure measures.

We used Cox regression models to calculate hazard ratios (95% confidence intervals) of incident clinical AAA according to presence/absence of carotid plaque or across quartiles of cIMT and Beta Index. Follow-up time was calculated from Visit 1 for carotid plaque analysis and cIMT analysis while from Visit 2 for carotid distensibility analysis. A trend test across quartiles was calculated using the ordinal number for quartiles as a continuous variable in the Cox models. The assumption of proportional hazard was examined by testing the

interaction for exposure variable by time. Schoenfeld residuals were checked for testing the proportional hazard assumption.

For analysis of ultrasound-detected AAA, we performed weighted general estimating equation regression. Given that 40% of the cohort were either lost to follow-up or died prior to the ultrasound exam at Visit 5, attrition yielded differential participation in the Visit 5 exam based on exposure status and AAA occurrence. To reduce the potential selection bias in the ultrasound AAA analysis, we used inverse probability of attrition weighting (IPAW) to account for attrition. As previously described,[148] the weights were calculated based on the product of the probability of being alive at Visit 5 and the probability of having an abdominal ultrasound conditional on being alive given a variety of covariates measured at baseline and during follow-up. Regression coefficients to calculate odds ratios and their 95% CIs were obtained from IPAW general estimating equation models. The basic models to test our hypotheses were adjusted for age, sex, race, and ARIC field center. The additional models (i.e., fully adjusted models) were further adjusted for baseline height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes. In addition, interactions by sex or race in the association of cIMT, plaque, and Beta Index with AAA were explored.

We conducted several sensitivity analyses to test robustness of study results.

1. Given that there was no ultrasound examination available to identify prevalent AAAs at baseline, to address the possibility of reverse causality, we performed a secondary analysis by excluding AAAs ascertained during the first 10 years of follow-up.

2. Since Medicare outpatient claims have unknown validity in the diagnosis of AAA, we also performed a sensitivity analysis by excluding outpatient AAAs which were not verified by hospitalization records, death records, or the ultrasound exam.

3. Additional sensitivity analyses included further adjustment for Visit 1 fibrinogen or white blood cell count, which were novel cardiovascular biomarkers related to homeostasis and both have been associated with AAA in ARIC (also known to related to atherosclerosis).[51]

4. Adiposity and diastolic blood pressure appears to be associated with AAA although it is not a well-established AAA risk factor.[52,149] However, it is worth to evaluate the potential impact of these variables. We performed sensitivity analyses by further adjusting for body mass index, waist circumference, and diastolic blood pressure in turn in the fully adjusted models for the clinical AAA analysis

5. In the previous study conducted in ARIC, alcohol or triglycerides was not significantly associated with clinical AAA ($P > 0.50$ for both in fully adjusted model), and triglycerides and alcohol were associated with ultrasound AAA at

borderline significance (P = 0.07 for triglycerides and P = 0.20 for alcohol).[52] Therefore, we did not include them for the adjustments in the analyses of clinical AAAs in the primary analysis but conduct a sensitivity analysis by further adjusting for alcohol consumption and triglycerides in the fully adjusted models of the clinical AAA analysis

6. We conducted the following analyses to account for competing risks of atherosclerotic cardiovascular disease and death: **a)** excluded prevalent coronary heart disease, stroke, and myocardial infarction at baseline; **b)** used a cause-specific Cox regression model where each participant was classified as either an AAA event, censored, or a cardiovascular disease event, whichever occurred first;[150-153] the time to the first event, either an AAA or another cardiovascular event, was considered the failure time. If an AAA event occurred on the same day as the day of other CVD events, which may rarely happen, the AAA event was coded as occurring first. In the competing risks models, the time to the first event, either an AAA or another CVD event, was considered the failure time. The competing incidence rate was calculated as the product of the hazard and the event-free survival time, both of which were obtained from the cause-specific models. Thus, hazard ratios for competing AAA compared with other CVD event for each comparison was estimated; **c)** repeated analysis b) using death instead of cardiovascular event.[152,153]

7. Finally, we included cIMT and Beta Index simultaneously in the fully-adjusted models to evaluate the independence of these two indices in their associations with AAA.

3.3 Results

3.3.1 Baseline description

At Visit 1 in 1987 - 89, the mean age of this ARIC sample (N = 14,573) at risk of AAA was 54.2 years (SD 5.8); 45% were male and 73% were white. Approximately 34.2% of participants had carotid plaque. As shown in **Table 3.3**, on average, participants in the higher quartiles of cIMT were older, more often male, non-white, current/former smokers, hypertensive, diabetic, had carotid plaque, had lower levels of high-density lipoprotein cholesterol, and had higher levels of weight, body mass index, total cholesterol, systolic/diastolic blood pressure, fibrinogen, white blood cell count, and Beta Index (all P for trend < 0.0001). The pattern of risk factor associations with Beta Index at Visit 2 was similar to that for cIMT with the exception that white blood cell count was not associated with Beta Index and smoking was inversely associated with Beta Index **(Table 3.4).**

3.3.2 Carotid atherosclerosis in relation to AAA

During a median of 22.5 years of follow-up through 2011, 542 clinical AAAs were ascertained. A linear relationship between cIMT and risk of incident clinical AAA was indicated by cubic spline analyses (**Figure 3.2**). Distributions of

Schoefeld residuals of cIMT and carotid plaque over time appeared to be roughly random (**Figures 3.3 and 3.4**). In addition, the interaction term of cIMT or plaque by time was not significant in the Cox model including time interaction terms (**Table 3.5**). Both evidence suggested that proportional hazard assumption is not violated.

Similar to the pattern observed on Kaplan-Meier curves (**Figure 3.5**), participants in the highest quartile of cIMT (> 0.82 mm) had 2.71-fold increased risk of incident clinical AAA [95% CI: 2.01, 3.67], compared to the lowest quartile, after adjustment for age, sex, race, and ARIC field center (P for trend < 0.0001) in Cox proportional hazard regression analysis (**Table 3.6**). With further adjustment for other risk factors (Model 2), a linear relationship remained (P for trend: 0.006; hazard ratio [95% CI] for the highest vs. lowest quartiles of cIMT: 1.55 [1.13, 2.11]). Participants who had a carotid plaque had 1.31 (95% CI: 1.10, 1.57; P: 0.003) times higher risk of incident clinical AAA than those without a plaque in the fully adjusted model (**Table 3.7**).

Of 5,459 participants who attended the ultrasound exam in 2011-13, 69 asymptomatic AAAs were detected. In the basic model adjusting for age, sex, and race, cIMT was positively, albeit not significantly, associated with asymptomatic AAAs (P for trend: 0.44; odds ratio [95% CI] for the highest vs lowest quartile of cIMT: 1.61 [0.47, 5.45]) (**Table 3.8**). Presence of carotid plaque was associated with 2.62 (95% CI: 1.01, 6.83; P: 0.04) times higher risk of asymptomatic AAAs than those without a plaque in the basic model (**Table 3.9**).

The association between carotid plaque and ultrasound-measured AAA was slightly attenuated in the fully adjusted model (odds ratio: 2.17; 95% CI: 0.71, 6.42; P: 0.18).

3.3.3 Carotid artery distensibility in relation to AAA

A linear relation between Beta Index and risk of incident clinical AAA was indicated by restricted cubic spline (**Figure 3.6**). Distributions of Schoefeld residuals of Beta Index over time appeared to be random (**Figure 3.7**). In addition, the interaction term of Beta Index by time was not significant (**Table 3.5**). Both evidence suggested that proportional hazard assumption is met.

Consistent with the pattern shown on the Kaplan-Meier curves (**Figure 3.8**), there was a positive association between Beta Index quartiles and clinical AAA in the fully adjusted model (P for trend 0.006); participants in the highest quartile of the Beta Index (> 13.05), indicating less carotid distensibility, had 1.68 (95% CI: 1.16, 2.43) times higher risk of incident clinical AAA compared to those in the lowest quartile (**Table 3.10**).

The association of Beta Index with asymptomatic AAAs was also positive, albeit not statistically significant, in the basic model (P for trend 0.22; odds ratio [95% CI] for the highest vs. lowest quartiles of Beta Index: 1.44 [0.32, 6.59]) (**Table 3.11**).

The above associations for all of the three carotid measures did not differ significantly by sex or race (All P values > 0.05; **Table 3.12**).

3.3.4 Sensitivity analyses

The associations of AAA with cIMT, carotid plaque, and Beta Index were similar in our sensitivity analysis after excluding AAAs occurring in the first 10 years of follow-up. For example, in the fully adjusted model, the hazard ratio of incident clinical AAA for carotid plaque presence vs. absence was 1.38 (95% CI: 1.13, 1.68, P: 0.002); the hazard ratio (95% CI) of incident clinical AAAs for the highest vs. lowest quartile of cIMT was 1.47 (1.05, 2.05) and P for trend was 0.03; the hazard ratio (95% CI) of incident clinical AAAs for the highest vs. lowest quartile of Beta Index was 1.49 [1.01, 2.20], and P for trend was 0.04. Results remained consistent after removing 101 Medicare outpatient AAAs who were not verified by hospitalization/death records or ultrasound exam (**Tables 3.13 - 3.15**); additionally adjusting for white blood cell count, fibrinogen, waist circumference, body mass index, diastolic blood pressure, triglycerides, or alcohol intake did not materially change the associations of any of the three carotid measures with AAA risk (**Tables 3.16 - 3.23**) In the competing risk analyses, consistent results were observed after accounting for the competing risk of cardiovascular events or death; the associations became slightly stronger after excluding prevalent cardiovascular disease at baseline (**Tables 3.24 - 3.32**). Furthermore, in the fully adjusted model, the associations of cIMT and Beta Index with AAA risk remained significant with mutual adjustment for each other (**Table 3.33**).

3.4 Discussion

This population-based prospective study showed that carotid atherosclerosis as represented by greater cIMT or presence of plaque and carotid stiffness as represented by reduced carotid artery distensibility were associated with higher risk of clinically detected, incident AAA. Associations were in the same direction for ultrasound-detected AAAs though most of these associations were not statistically significant, likely due to the low number of asymptomatic AAAs detected from the Visit 5 exam. Our findings indicate that persons with carotid atherosclerosis or 'stiff' carotid arteries are at a higher risk for AAA than those without these conditions. This information might be useful in consideration of a prediction model to identify high risk individuals for AAA screening.

Although an atherosclerosis-AAA association has not been directly documented in previous epidemiological studies, a dose-response relationship between atherosclerosis as reflected by carotid total plaque area and maximal abdominal aortic diameter was reported in a cross-sectional survey including Norwegians aged 55 to 74 years with and without AAA.[113] A follow-up study of 2019 persons in that sample showed that one-standard-deviation increase in carotid plaque area was associated with 0.12 mm concurrent growth in average infrarenal aortic diameter over 6 - 7 years (including 130 AAAs).[55] In contrast, our study prospectively examined the association between baseline carotid ultrasound and a large number of incident AAAs ascertained over two decades.

Our findings suggest that subclinical carotid atherosclerosis is a risk marker for clinical AAA. Although any biological link is indirect, because we assessed atherosclerosis in the carotids, not the abdominal aorta, it is well known that atherosclerosis is typically widespread throughout the vasculature.[140] Therefore, the association observed in our study likely reflects a relation between general atherosclerosis and AAA occurrence.

With regard to our findings that AAA is more likely to occur in the presence of subclinical atherosclerosis, data from animal studies have shown that aortic aneurysms often form after prolonged exposure to atherogenic conditions reflected by aortic atherosclerotic plaque.[98] Atherosclerotic plaques in the aortic wall include matrix fibers, and the expansion of plaques may simultaneously dilate and weaken aortic walls that support mural tension, potentially leading to aneurysmal enlargement.[98] Studies have demonstrated that atherosclerosis, although initially occurring in the intima, promotes the dilation or shrinkage of the tunica media and adventitia; this in turn aggravates luminal obstruction and promotes vascular remodeling via a disturbance in the synthesis and degradation of matrix proteins.[93,94] In addition, atherosclerotic plaques may be associated with later arterial dilation.[99] On the other hand, atherosclerosis clearly is not necessary for AAA formation. AAA can form with toxic exposure to smoking, or for instance, with hypertension, Marfan's syndrome, Chlamydia pneumoniae infection, or syphilis.[92] Thus, a link between atherosclerosis and AAA is largely

supported by physiological data but further pathological and epidemiological evidence is warranted to establish a causal relationship.

On the other hand, it may be that both atherosclerosis and AAA are the result of common risk factors or a common genetic predisposition (pleiotropy), and there is no direct pathophysiological connection of atherosclerosis with AAA. We adjusted for many AAA risk factors, but residual confounding may be present from measurement error in those risk factors or from failure to adjust for unrecognized or unmeasured AAA risk factors.

Concerning arterial stiffness and AAA, in vivo studies have shown a greater stiffness of dilated or aneurysmal aortic walls in AAAs.[154,155] As the pathogenesis of AAA is related to an alteration in systemic connective tissue metabolism, change in wall stiffness may occur in the rest of the vascular system, such as the carotid arteries, of AAA patients.[156] So far, only a small cross-sectional, hospital-based study reported that patients with AAA had a higher carotid artery Beta Index than did those without AAA.[141] In addition, carotid stiffness has been positively associated with abdominal aortic diameters both in AAAs and non-AAAs.[157,158] To our knowledge, our study is the first investigation showing that greater carotid stiffness is prospectively associated with higher risk of AAA in the general population. Findings from our study as well as the previous studies suggest that carotid stiffness index is a risk marker of AAA.

The inverse association between smoking (collected in 1990 - 92 at Visit 2) and Beta Index, suggesting that smoking is associated with more distensible

carotid arteries, was unexpected. A possible explanation is that some participants who had a more severe cardiovascular risk factor profile at Visit 1 may have stopped smoking around the Visit 2 exam. For example, we noticed that participants with prevalent hypertension smoked less compared to those without hypertension in ARIC Visit 2 (ever smoker 57% vs. 60%; P for difference < 0.001); a similar pattern was also observed for prevalent diabetes (ever smoker 56% vs. 59%; P for difference < 0.001). Future research is warranted to clarify this issue.

The strengths of our study include the prospective design, high quality measurements of exposures and outcomes, and a large sample size with a large number of incident AAAs. Nonetheless, the following limitations should be acknowledged when interpreting our results. First, misclassification may have occurred. Misclassification in the carotid ultrasound measures would likely have been non-differential with respect to AAA status given the prospective design of our study. Misclassification in the AAA outcomes would also likely have been non-differential, since staff who ascertained AAAs in ARIC were blinded to the exposure status. Non-differential misclassifications most likely would have diluted the estimates of association between AAA and exposures. Second, as noted above and as in other observational studies, residual confounding cannot be eliminated. Third, the clinical AAAs were ascertained based on ICD codes, and thus included both symptomatic and medically documented, asymptomatic AAAs. Fourth, since there was no baseline ultrasound exam for AAA, we cannot verify

that atherosclerosis and carotid stiffness always preceded incident AAA. However, participants who had AAAs through ARIC Visit 5 were likely free of AAA when they were aged 45-64 years at baseline considering the low prevalence of AAAs in that age group (about 1.8% in men and 0.2% in women).[23] Our sensitivity analysis excluding clinical AAAs ascertained within 10 years of baseline showed similar results to our main analysis. Moreover, analysis of ultrasound-detected AAA has the following additional limitations. Since ultrasound was measured only once in 2011-13, it is impossible to determine time of incidence for ultrasound-measured AAAs. In addition, the analysis of ultrasound-detected AAAs, restricted to the surviving subsample of ARIC population, may be biased by attrition if the attrition was differential with regard to subclinical atherosclerosis markers and AAA outcome; however, we observed that the associations for ultrasound-detected AAA were in the same direction as those for clinical AAAs after accounting for attrition using the IPAW methods. The non-significant associations for ultrasound-detected AAAs may result from insufficient power due to their limited number.

In conclusion, this large, population-based cohort study, with more than 20 years of follow-up, showed that carotid atherosclerosis and stiffness were associated positively with future risk of AAA, independent of traditional risk factors for atherosclerosis and AAA. The association likely reflects the underlying link between general atherosclerosis, arterial stiffness, and AAA or the impact of risk factors common to AAA and these conditions.

3.5 Tables

Table 3.1 Distribution of indices of carotid artery distensibility

Variable	N	Mean	Standard deviation	Minimum	Maximum
Carotid arterial strain	10337	0.053	0.018	0.001	0.153
Young's elastic modulus	10055	752	364	108	3026
Arterial diameter change	10338	399	128	10	1130
Peterson's elastic modulus	10324	1102	605	81	9088
Beta Index	10290	11.22	4.63	2.83	44.49

Table 3.2 Correlation coefficients among indices of carotid artery distensibility

		Carotid arterial strain	Young's elastic modulus	Arterial diameter change	Peterson's elastic modulus	Beta Index
Carotid arterial strain	Pearson r	1	-0.62	0.92	-0.64	-0.73
	P value		<.0001	<.0001	<.0001	<.0001
N=	N	10337	10053	10336	10322	10288
Young's elastic modulus	Pearson r	-0.62	1	-0.53	0.74	0.78
	P value	<.0001		<.0001	<.0001	<.0001
	N	10053	10055	10054	10041	10013
Arterial diameter change	Pearson r	0.92	-0.53	1	-0.57	-0.67
	P value	<.0001	<.0001		<.0001	<.0001
	N	10336	10054	10338	10323	10289
Peterson's elastic	Pearson r	-0.64	0.74	-0.57	1	0.95

modulus	P value	<.0001	<.0001	<.0001		<.0001
	N	10322	10041	10323	10324	10290
	Pearson r	-0.73	0.78	-0.67	0.95	1
Beta Index	P value	<.0001	<.0001	<.0001	<.0001	
	N	10288	10013	10289	10290	10290

Table 3.3 Baseline characteristics by quartiles of carotid intima-media thickness (cIMT), ARIC, 1987 - 89

Characteristics [a]	cIMT quartile				P for trend
	1	2	3	4	
	N = 3643	N = 3643	N = 3644	N = 3643	
cIMT median, mm	0.59	0.67	0.76	0.93	
cIMT range, mm	0.37 - 0.63	0.64 - 0.71	0.72 - 0.82	0.83 - 2.26	
Carotid plaque, %	431 (11.8)	746 (20.5)	1279 (35.1)	2532 (69.5)	<0.0001
Age, years	51.6 (5.2)	53.4 (5.5)	54.8 (5.6)	57.0 (5.3)	<0.0001
Male, %	965 (26.5)	1395 (38.3)	1864 (51.2)	2297 (63.1)	<0.0001
White, %	2878 (79.0)	2642 (72.5)	2612 (71.7)	2705 (74.3)	<0.0001
Height, cm	166.3 (8.7)	167.8 (9.2)	169.5 (9.4)	170.5 (9.2)	<0.0001
Weight, kg	72.5 (15.5)	77.7 (15.8)	80.9 (16.5)	81.4 (16.2)	<0.0001
Body mass index, kg/m^2	26.2 (5.0)	27.5 (5.1)	28.1 (5.2)	28.0 (4.9)	<0.0001
Smoking status					<0.0001

Current smoker, %	833 (22.9)	881 (24.2)	930 (25.6)	1185 (32.5)	
Former smoker, %	970 (26.7)	1090 (30.0)	1221 (33.5)	1415 (38.9)	
Never smoker, %	1837 (50.4)	1669 (45.8)	1490 (40.9)	1042 (28.6)	
Pack-years among smokers	21.6 (17.6)	24.6 (19.9)	28.8 (22.7)	34.9 (24.3)	<0.0001
Total cholesterol, mg/dL	205.5 (40.2)	213.3 (40.7)	217.1 (41.3)	222.2 (42.7)	<0.0001
High-density lipoprotein cholesterol, mg/dL	56.8 (17.7)	53.3 (17.9)	49.9 (16.1)	47.2 (15.4)	<0.0001
Lipid lowering medication, %	73 (2.0)	87 (2.4)	105 (2.9)	150 (4.2)	<0.0001
Systolic blood pressure, mmHg	114.7 (16.7)	119.2 (17.1)	122.7 (18.0)	127.6 (20.5)	<0.0001
Hypertensive medication use, %	751 (20.6)	1018 (28.0)	1160 (31.8)	1411 (38.8)	<0.0001
Diabetes, %	190 (5.3)	345 (9.6)	440 (12.2)	650 (18.0)	<0.0001
Fibrinogen, mg/dL	292.9 (58.4)	298.8 (63.4)	302.5 (64.4)	316.3 (71.1)	<0.0001
White blood cell count, 1000 cells/mm^3	5.9 (1.9)	6.0 (1.9)	6.1 (1.9)	6.5 (2.1)	<0.0001
Beta Index [b]	10.0 (3.7)	10.8 (4.1)	11.5 (4.6)	12.7 (5.6)	<0.0001

[a] Mean (SD) for continuous variables or N (%) for categorical variables;

[b] Beta index was measured in 1990 - 92.

Table 3.4 Baseline characteristics by quartiles of Beta Index, ARIC, 1990 - 92

Characteristics [a]	Beta Index levels				P for trend
	Quartile 1 N = 2572	Quartile 2 N = 2573	Quartile 3 N = 2573	Quartile 4 N = 2572	
Beta Index median, mm [b]	6.93	9.20	11.48	15.91	
Beta Index range, mm	2.83 - 8.17	8.18 - 10.28	10.29 - 13.05	13.06 - 44.49	
Age, year	54.0 (4.9)	56.0 (5.5)	57.5 (5.6)	59.5 (5.3)	<0.0001
Male, %	1200 (46.7)	1170 (45.5)	1093 (42.5)	1048 (40.8)	<0.0001
White, %	2018 (78.5)	1906 (74.1)	1927 (74.9)	1861 (72.4)	<0.0001
Height, cm	169.6 (9.2)	169.0 (9.3)	168.2 (9.3)	167.4 (9.2)	<0.0001
Weight, kg	75.1 (14.4)	77.6 (15.8)	78.8 (16.0)	80.2 (16.4)	<0.0001
Body mass index, kg/m^2	26.0 (4.1)	27.1 (4.6)	27.8 (5.0)	28.6 (5.3)	<0.0001
Smoking status					<0.0001
Current smoker, %	748 (29.1)	564 (21.9)	487 (18.9)	428 (16.6)	

Former smoker, %	898 (34.9)	981 (38.1)	972 (37.8)	1007 (39.2)	
Never smoker, %	925 (36.0)	1028 (40.0)	1112 (43.3)	1135 (44.2)	
Smoking among smokers, pack-year	52.3 (47.5)	46.6 (44.4)	45.2 (45.1)	42.3 (42.1)	<0.0001
Total cholesterol, mg/dL	204.2 (37.3)	207.4 (37.6)	210.7 (39.0)	214.4 (41.4)	<0.0001
High-density lipoprotein cholesterol, mg/dL	51.1 (16.7)	50.5 (17.0)	50.2 (16.9)	48.9 (16.6)	<0.0001
Lipid lowering medication, %	128 (5.0)	150 (5.8)	149 (5.8)	190 (7.4)	0.0006
Systolic blood pressure, mmHg	114.0 (15.0)	118.6 (16.6)	122.3 (17.8)	127.7 (20.2)	<0.0001
Antihypertensive medication, %	515 (20.0)	716 (27.8)	828 (32.2)	1041 (40.5)	<0.0001
Type-2 Diabetes, %	184 (7.2)	258 (10.1)	337 (13.2)	542 (21.2)	<0.0001
Carotid intima-media thickness, mm [c]	0.70 (0.15)	0.73 (0.18)	0.74 (0.18)	0.79 (0.21)	
Fibrinogen, mg/dL [d]	290.1 (60.5)	295.6 (62.6)	301.7 (60.1)	306.2 (63.2)	<0.0001
White blood cell count, 1000 cells/mm^3 [d]	6.0 (1.9)	6.0 (2.1)	6.0 (1.9)	6.0 (2.2)	0.46

[a] Mean (standard deviation) for continuous variables or N (%) for categorical variables;

[b] Higher level of the Beta Index indicates less carotid artery distensibility;

[c] Carotid intima-media thickness, measured in ARIC Visit 2, 1990 - 92;

[d] Measured at ARIC Visit 1, 1987 - 89.

Table 3.5 Estimates of Cox model with time-dependent variables for linearity test

Interaction term by follow up time	Parameter	Standard error	Chi-square	P
Carotid intima-media thickness * time	-0.1667	0.23406	0.5072	0.48
Plaque * time	0.03911	0.14195	0.0759	0.78
Beta Index * time	-0.0128	0.01656	0.6001	0.44

[a] For Carotid intima-media thickness or plaque as the exposure variable, the models also were adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, diabetes and their time-interaction terms at ARIC Visit 1;

[b] For Beta Index as the exposure variable, the models were also adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, diabetes and their time interaction terms at ARIC Visit 2.

Table 3.6 Risk of clinical abdominal aortic aneurysm in relation to quartiles of carotid intima-media thickness (cIMT), ARIC, 1987 - 2011

cIMT	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Quartile range, mm	0.37 - 0.63	0.64 - 0.71	0.72 - 0.82	0.83 - 2.26	
N at risk	3643	3644	3644	3644	
No. events	59	95	139	249	
Incidence rate [a]	0.76 (0.59, 0.98)	1.26 (1.03, 1.55)	1.92 (1.63, 2.27)	3.90 (3.45, 4.42)	
HR (95% CI)					
Model 1 [b]	1	1.32 (0.96, 1.84)	1.62 (1.18, 2.21)	2.71 (2.01, 3.67)	<0.0001
Model 2 [c]	1	1.11 (0.80, 1.54)	1.15 (0.84, 1.59)	1.55 (1.13, 2.11)	0.006

CI, confidence interval; HR, hazard ratio;

[a] Crude incidence rate per 1000 person-years;

[b] Model 1: Adjusted for age, sex, race, and ARIC center;

[c] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1.

Table 3.7 Risk of clinical abdominal aortic aneurysm in relation to presence vs. absence of carotid plaque, ARIC, 1987 - 2011

Plaque (y/n)	Absence	Presence	P value
N at risk	9596	4989	
No. events	259	283	
Incidence rate [a]	1.31 (1.16, 1.48)	3.11 (2.77, 3.49)	
HR (95% CI)			
Model 1 [b]	1	1.82 (1.53, 2.17)	<0.0001
Model 2 [c]	1	1.31 (1.10, 1.57)	0.003

[a] Crude incidence rate per 1000 person-years;

[b] Model 1: Adjusted for age, sex, race, and ARIC center;

[c] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1.

Table 3.8 Risk of asymptomatic abdominal aortic aneurysm diagnosed by ultrasound exam in 2011 - 13 in relation to quartiles of carotid intima-media thickness in 1987 - 92, ARIC.

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
cIMT	Quartile range, mm	0.41 - 0.63	0.64 - 0.71	0.72 - 0.82	0.83 - 1.65	
	N at risk	1883	1508	1273	795	
	No. events	16	12	20	21	
	OR (95% CI) [a]	1	0.79 (0.26, 2.39)	1.83 (0.59, 5.65)	1.61 (0.47, 5.45)	0.44

CI, confidence interval; cIMT, carotid intima-media thickness; OR, odds ratio

[a] Adjusted for age, sex and race.

Table 3.9 Risk of asymptomatic abdominal aortic aneurysm diagnosed by ultrasound exam in 2011-2013 in relation to presence vs. absence of carotid plaque in 1987 - 89, ARIC

		Absence	Presence	P value
Plaque (y/n)	N at risk	4077	1363	
	N event (%)	37 (0.9)	32 (2.3)	
	OR (95% CI) [a]	1	2.62 (1.01, 6.83)	0.04

CI, confidence interval; OR, odds ratio;

[a] Adjusted for age, sex, and race.

Table 3.10 Risk of clinical abdominal aortic aneurysm in relation to quartiles of Beta Index of the carotid artery, ARIC, 1990 - 2011

Beta Index [a]	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Quartile Range	2.83 - 8.17	8.18 - 10.28	10.29 - 13.05	13.06 - 44.49	
N at risk	2572	2573	2573	2572	
No. events	50	89	102	111	
Incidence rate [b]	1.05 (0.79, 1.38)	1.91 (1.55, 2.35)	2.25 (1.85, 2.73)	2.55 (2.12, 3.07)	
HR (95% CI)					
Model 1 [c]	1	1.58 (1.11, 2.24)	1.68 (1.19, 2.38)	1.72 (1.21, 2.44)	0.003
Model 2 [d]	1	1.61 (1.12, 2.31)	1.62 (1.12, 2.33)	1.68 (1.16, 2.43)	0.006

CI, confidence interval; HR, hazard ratio;

[a] Higher level of the Beta Index indicates less carotid artery distensibility;

[b] Crude incidence rate per 1000 person-years;

[c] Model 1: Adjusted for age, sex, race, and ARIC center;

[d] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 2.

Table 3.11 Risk of asymptomatic abdominal aortic aneurysm diagnosed by ultrasound exam in 2011 - 13 in relation to quartiles of Beta stiffness index in 1990 - 92, ARIC.

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Beta index [a]	Quartile Range	2.83 - 8.17	8.18 - 10.28	10.29 - 13.05	13.06 – 40.37	
	N at risk	1336	1173	1035	807	
	No. events	12	15	16	15	
	OR (95% CI) [b]	1	1.14 (0.36, 3.64)	0.96 (0.22, 4.24)	1.44 (0.32, 6.59)	0.22

CI, confidence interval; OR, odds ratio

[a] Higher level of the Beta Index indicates less carotid artery distensibility;

[b] Adjusted for age, sex and race.

Table 3.12 P values for interactions by race and sex in the association of carotid intima-media thinkness (cIMT), plaque and Beta Index with clinical abdominal aortic aneurysm.

Interaction term	P values for interaction		
	cIMT	**Plaque**	**Beta-Index**
By sex	0.69	0.07	0.60
By race	0.60	0.17	0.79

All models included an interaction term by sex or by race, with adjustment for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes.

Table 3.13 Risk of clinical abdominal aortic aneurysm in relation to quartiles of carotid intima-media thickness (cIMT) after excluding outpatients only ascertained by Medicare database, ARIC, 1987 - 2011

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
cIMT	Quartile range, mm	0.37 - 0.63	0.64 - 0.71	0.72 - 0.82	0.83 - 2.26	
	N at risk	3643	3643	3644	3643	
	No. events	49	76	108	208	
	Incidence rate, 1000 person-years [a,b]	0.59 (0.45, 0.78)	0.95 (0.76, 1.19)	1.41 (1.17, 1.71)	3.12 (2.73, 3.58)	
	Model 1 HR (95% CI) [b]	1	1.27 (0.88, 1.82)	1.49 (1.06, 2.11)	2.67 (1.91, 3.71)	<0.0001
	Model 2 HR (95% CI) [c]	1	1.04 (0.72, 1.50)	1.02 (0.71, 1.45)	1.44 (1.02, 2.02)	0.04

CI, confidence interval; HR, hazard ratio

[a] Incidence rate per 1000 person-years.

[b] Model 1: Adjusted for age, sex, race, and ARIC center

[c] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1

Table 3.14 Risk of clinical abdominal aortic aneurysm in relation to presence vs. absence of carotid plaque after excluding outpatients only ascertained by Medicare database, ARIC, 1987 - 2011

		Absence	Presence	P value
Plaque (y/n)	N at risk	9595	4988	
	No. events	211	230	
	Incidence rate, 1000 person-years [a]	1.00 (0.88, 1.15)	2.41 (2.11, 2.74)	
	Model 1 HR [a]	1	1.80 (1.49, 2.18)	<0.0001
	Model 2 HR [b]	1	1.27 (1.04, 1.55)	0.02

[a] Model 1: Adjusted for age, sex, race, and ARIC center

[b] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1

Table 3.15 Risk of clinical abdominal aortic aneurysm in relation to quartiles of Beta stiffness index of the carotid artery after excluding outpatients only ascertained by Medicare database, ARIC, 1990 - 2011

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Beta	Quartile Range	2.83 - 8.17	8.18 - 10.28	10.29 - 13.05	13.06 - 44.49	
Index [a]	N at risk	2572	2573	2573	2572	
	No. events	39	71	83	88	
	Incidence rate, 1000 person-years [b,c]	0.82 (0.60, 1.12)	1.52 (1.21, 1.92)	1.83 (1.48, 2.27)	2.02 (1.64, 2.49)	
	Model 1 HR (95% CI) [c]	1	1.61 (1.09, 2.39)	1.76 (1.19, 2.60)	1.76 (1.18, 2.60)	0.005
	Model 2 HR (95% CI) [d]	1	1.67 (1.11, 2.52)	1.73 (1.15, 2.62)	1.73 (1.14, 2.64)	0.01

CI, confidence interval; HR, hazard ratio

[a] Higher level of the Beta Index indicates less carotid artery distensibility;

[b] Incidence rate per 1000 person-years.

[c] Model 1: Adjusted for age, sex, race, and ARIC center

[d] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC visit 2.

Table 3.16 Risk of clinical abdominal aortic aneurysm in relation to quartiles of carotid intima-media thickness (cIMT) and quartiles of Beta Index before and after further adjustment for waist circumference, ARIC, 1987 - 2011

Exposure variable		Hazard ratio (95%CI) [a,b]				P for trend
		Q1	Q2	Q3	Q4	
cIMT	Not adjusted for WC	1	1.11 (0.80, 1.54)	1.15 (0.84, 1.59)	1.55 (1.13, 2.11)	0.006
	Adjusted for WC	1	1.12 (0.81, 1.56)	1.18 (0.86, 1.63)	1.58 (1.16, 2.16)	0.004
Beta Index	Not adjusted for WC	1	1.61 (1.12, 2.31)	1.62 (1.12, 2.33)	1.68 (1.16, 2.43)	0.006
	Adjusted for WC	1	1.63 (1.13, 2.34)	1.63 (1.13, 2.36)	1.70 (1.17, 2.47)	0.006

[a] For cIMT as the exposure variable, the models also were adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1;

[b] For Beta Index as the exposure variable, the models were also adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 2.

Table 3.17 Risk of clinical abdominal aortic aneurysm in relation to presence of carotid atherosclerotic plaque before and after further adjustment for waist circumference, ARIC, 1987 - 2011

Exposure		Hazard ratio (95% CI) [a]		P for difference
		Absence	Presence	
Plaque	Not adjusted for WC	1	1.31 (1.10, 1.57)	0.003
	Adjusted for WC	1	1.30 (1.09, 1.56)	0.004

[a] The models were also adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1.

Table 3.18 Risk of clinical abdominal aortic aneurysm in relation to quartiles of carotid intima-media thickness (cIMT) and quartiles of Beta Index before and after further adjustment for diastolic blood pressure, ARIC, 1987 - 2011

Exposure variable		Hazard ratio (95%CI) [a,b]				P for trend
		Q1	Q2	Q3	Q4	
cIMT	Not adjusted for DBP	1	1.11 (0.80, 1.54)	1.15 (0.84, 1.59)	1.55 (1.13, 2.11)	0.006
	Adjusted for DBP	1	1.10 (0.79, 1.53)	1.15 (0.84, 1.59)	1.56 (1.14, 2.12)	0.005
Beta Index	Not adjusted for	1	1.61	1.62	1.68	0.006

DBP		(1.12, 2.31)	(1.12, 2.33)	(1.16, 2.43)	
Adjusted for DBP	1	1.57	1.56	1.56	0.02
		(1.09, 2.25)	(1.08, 2.25)	(1.07, 2.27)	

[a] For cIMT as the exposure variable, the models also were adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1;

[b] For Beta Index as the exposure variable, the models were also adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 2.

Table 3.19 Risk of clinical abdominal aortic aneurysm in relation to presence of carotid atherosclerotic plaque before and after further adjustment for diastolic blood pressure, ARIC, 1987 - 2011

Exposure		Hazard ratio (95% CI) [a]		P for difference
		Absence	Presence	
Plaque	Not adjusted for DBP	1	1.31 (1.10, 1.57)	0.003
	Adjusted for DBP	1	1.34 (1.12, 1.60)	0.002

[a] The models were also adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1.

Table 3.20 Risk of clinical abdominal aortic aneurysm in relation to quartiles of carotid intima-media thickness (cIMT) and quartiles of Beta Index before and after further adjustment for body mass index, ARIC, 1987 - 2011

Exposure variable		Hazard ratio (95%CI) [a,b]				P for trend
		Q1	Q2	Q3	Q4	
cIMT	Not adjusted for BMI	1	1.11 (0.80, 1.54)	1.15 (0.84, 1.59)	1.55 (1.13, 2.11)	0.006
	Adjusted for BMI	1	1.11 (0.80, 1.55)	1.17 (0.85, 1.61)	1.57 (1.15, 2.14)	0.005
Beta Index	Not adjusted for BMI	1	1.61 (1.12, 2.31)	1.62 (1.12, 2.33)	1.68 (1.16, 2.43)	0.006
	Adjusted for BMI	1	1.63	1.64	1.72	0.005

	(1.14, 2.35)	(1.14, 2.37)	(1.18, 2.50)

[a] For cIMT as the exposure variable, the models also were adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1;

[b] For Beta Index as the exposure variable, the models were also adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 2.

Table 3.21 Risk of clinical abdominal aortic aneurysm in relation to presence of carotid atherosclerotic plaque before and after further adjustment for body mass index, ARIC, 1987 - 2011

Exposure		Hazard ratio (95% CI) [a]		P for difference
		Absence	Presence	
Plaque	Not adjusted for BMI	1	1.31 (1.10, 1.57)	0.003
	Adjusted for BMI	1	1.31 (1.09, 1.56)	0.004

[a] The models were also adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1.

Table 3.22 Risk of clinical abdominal aortic aneurysm in relation to quartiles of carotid intima-media thickness (cIMT) and quartiles of Beta Index before and after further adjustment for alcohol and triglycerides (TG), ARIC, 1987 - 2011

Exposure variable		Hazard ratio (95%CI) [a,b]				P for trend
		Q1	Q2	Q3	Q4	
cIMT	Not adjusted for alcohol and TG	1	1.11 (0.80, 1.54)	1.15 (0.84, 1.59)	1.55 (1.13, 2.11)	0.006
	Adjusted for alcohol and TG	1	1.07 (0.77, 1.50)	1.12 (0.81, 1.54)	1.53 (1.12, 2.10)	0.007
Beta Index	Not adjusted for	1	1.61	1.62	1.68	0.006

	alcohol and TG		(1.12, 2.31)	(1.12, 2.33)	(1.16, 2.43)	
	Adjusted for alcohol and TG	1	1.62 (1.13, 2.34)	1.63 (1.13, 2.35)	1.69 (1.17, 2.46)	0.006

[a] For cIMT as the exposure variable, the models also were adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1;

[b] For Beta Index as the exposure variable, the models were also adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 2.

Table 3.23 Risk of clinical abdominal aortic aneurysm in relation to presence of carotid atherosclerotic plaque before and after further adjustment for alcohol and triglycerides (TG), ARIC, 1987 - 2011

Exposure		Hazard ratio (95% CI) [a]		P for difference
		Absence	Presence	
Plaque	Not adjusted for alcohol and TG	1	1.31 (1.10, 1.57)	0.003
	Adjusted for alcohol and TG	1	1.33 (1.11, 1.59)	0.002

[a] The models were also adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1.

Table 3.24 Risk of clinical abdominal aortic aneurysm in relation to quartiles of carotid intima-media thickness (cIMT) after adjustment for competing risk of cardiovascular event, ARIC, 1987 - 2011

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
cIMT	Quartile range, mm	0.37 - 0.63	0.64 - 0.71	0.72 - 0.82	0.83 - 2.26	
	N at risk	3643	3644	3644	3644	
	No. events	59	95	139	249	
	Incidence rate, 1000 person-years [a,b]	0.76 (0.59, 0.98)	1.26 (1.03, 1.55)	1.92 (1.63, 2.27)	3.90 (3.45, 4.42)	
	Model 1 HR (95% CI) [b]	1	1.31 (0.95, 1.82)	1.58 (1.15, 2.17)	2.44 (1.79, 3.33)	<0.0001
	Model 2 HR (95% CI) [c]	1	1.13 (0.81, 1.57)	1.20 (0.87, 1.65)	1.50 (1.09, 2.05)	0.01

CI, confidence interval; HR, hazard ratio

[a] Incidence rate per 1000 person-years.

[b] Model 1: Adjusted for age, sex, race, and ARIC center

[c] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1

Table 3.25 Risk of clinical abdominal aortic aneurysm in relation to presence vs. absence of carotid plaque after adjustment for competing risk of cardiovascular event, ARIC, 1987 - 2011

		Absence	Presence	P value
Plaque (y/n)	N at risk	9596	4989	
	No. events	259	283	
	Incidence rate, 1000 person-years [a]	1.31 (1.16, 1.48)	3.11 (2.77, 3.49)	
	Model 1 HR [a]	1	1.67 (1.40, 2.00)	<0.0001
	Model 2 HR [b]	1	1.21 (1.01, 1.46)	0.04

[a] Model 1: Adjusted for age, sex, race, and ARIC center

[b] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1

Table 3.26 Risk of clinical abdominal aortic aneurysm in relation to quartiles of Beta stiffness index of the carotid artery after adjustment for competing risk of cardiovascular event, ARIC, 1990 - 2011

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Beta	Quartile Range	2.83 - 8.17	8.18 - 10.28	10.29 - 13.05	13.06 - 44.49	
Index[a]	N at risk	2572	2573	2573	2572	
	No. events	50	89	102	111	
	Incidence rate, 1000 person-years [b,c]	1.05 (0.79, 1.38)	1.91 (1.55, 2.35)	2.25 (1.85, 2.73)	2.55 (2.12, 3.07)	
	Model 1 HR (95% CI) [c]	1	1.57 (1.11, 2.23)	1.67 (1.19, 2.38)	1.63 (1.15, 2.31)	0.006
	Model 2 HR (95% CI) [d]	1	1.63 (1.13, 2.34)	1.62 (1.12, 2.34)	1.61 (1.12, 2.33)	0.01

CI, confidence interval; HR, hazard ratio

[a] Higher level of the Beta Index indicates less carotid artery distensibility;

[b] Incidence rate per 1000 person-years.

[c] Model 1: Adjusted for age, sex, race, and ARIC center.

[d] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC visit 2.

Table 3.27 Risk of clinical abdominal aortic aneurysm in relation to quartiles of carotid intima-media thickness (cIMT) after adjustment for competing risk of death, ARIC, 1987 - 2011

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
cIMT	Quartile range, mm	0.37 - 0.63	0.64 - 0.71	0.72 - 0.82	0.83 - 2.26	
	N at risk	3643	3644	3644	3644	
	No. events	59	95	139	249	
	Incidence rate, 1000 person-years [a,b]	0.76 (0.59, 0.98)	1.26 (1.03, 1.55)	1.92 (1.63, 2.27)	3.90 (3.45, 4.42)	
	Model 1 HR (95% CI) [b]	1	1.30 (0.94, 1.81)	1.57 (1.14, 2.15)	2.30 (1.68, 3.13)	<0.0001
	Model 2 HR (95% CI) [c]	1	1.12 (0.81, 1.56)	1.19 (0.87, 1.64)	1.42 (1.04, 1.95)	0.03

CI, confidence interval; HR, hazard ratio

[a] Incidence rate per 1000 person-years.

[b] Model 1: Adjusted for age, sex, race, and ARIC center

[c] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1

Table 3.28 Risk of clinical abdominal aortic aneurysm in relation to presence vs. absence of carotid plaque after adjustment for competing risk of death, ARIC, 1987 - 2011

		Absence	Presence	P value
Plaque (y/n)	N at risk	9596	4989	
	No. events	259	283	
	Incidence rate, 1000 person-years [a]	1.31 (1.16, 1.48)	3.11 (2.77, 3.49)	
	Model 1 HR [a]	1	1.59 (1.33, 1.89)	<0.0001
	Model 2 HR [b]	1	1.17 (0.97, 1.42)	0.09

[a] Model 1: Adjusted for age, sex, race, and ARIC center.

[b] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1

Table 3.29 Risk of clinical abdominal aortic aneurysm in relation to quartiles of Beta stiffness index of the carotid artery after adjustment for competing risk of death, ARIC, 1990 - 2011

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Beta	Quartile Range	2.83 - 8.17	8.18 - 10.28	10.29 - 13.05	13.06 - 44.49	
Index [a]	N at risk	2572	2573	2573	2572	
	No. events	50	89	102	111	
	Incidence rate, 1000 person-years [b,c]	1.05 (0.79, 1.38)	1.91 (1.55, 2.35)	2.25 (1.85, 2.73)	2.55 (2.12, 3.07)	
	Model 1 HR (95% CI) [c]	1	1.61 (1.13, 2.28)	1.69 (1.19, 2.39)	1.67 (1.17, 2.36)	0.004
	Model 2 HR (95% CI) [d]	1	1.66 (1.15, 2.38)	1.64 (1.13, 2.38)	1.64 (1.14, 2.37)	0.008

CI, confidence interval; HR, hazard ratio

[a] Higher level of the Beta Index indicates less carotid artery distensibility.

[b] Incidence rate per 1000 person-years.

[c] Model 1: Adjusted for age, sex, race, and ARIC center.

[d] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC visit 2.

Table 3.30 Risk of clinical abdominal aortic aneurysm in relation to quartiles of carotid intima-media thickness (cIMT) after excluding prevalent CVD events, ARIC, 1987 - 2011

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
cIMT	Quartile range, mm	0.37 - 0.63	0.64 - 0.71	0.72 - 0.82	0.83 - 2.26	
	N at risk	3538	3479	3428	3197	
	No. events	50	85	122	204	
	Incidence rate, 1000 person-years [a,b]	0.66 (0.50, 0.87)	1.17 (0.95, 1.45)	1.77 (1.48, 2.11)	3.54 (3.08, 4.06)	
	Model 1 HR (95% CI) [b]	1	1.42 (1.00, 2.01)	1.73 (1.23, 2.42)	2.85 (2.05, 3.95)	<0.0001
	Model 2 HR (95% CI) [c]	1	1.18 (0.83, 1.68)	1.24 (0.88, 1.75)	1.63 (1.16, 2.28)	0.004

CI, confidence interval; HR, hazard ratio

[a] Incidence rate per 1000 person-years.

[b] Model 1: Adjusted for age, sex, race, and ARIC center

[c] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1

Table 3.31 Risk of clinical abdominal aortic aneurysm in relation to presence vs. absence of carotid plaque after excluding prevalent CVD events, ARIC, 1987 - 2011

		Absence	Presence	P value
Plaque (y/n)	N at risk	9134	4508	
	No. events	226	235	
	Incidence rate, 1000 person-years [a]	1.19 (1.04, 1.35)	2.79 (2.45, 3.17)	
	Model 1 HR [a]	1	1.82 (1.51, 2.19)	<0.0001
	Model 2 HR [b]	1	1.31 (1.08, 1.59)	0.006

[a] Model 1: Adjusted for age, sex, race, and ARIC center.

[b] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1.

Table 3.32 Risk of clinical abdominal aortic aneurysm in relation to quartiles of Beta stiffness index of the carotid artery after excluding prevalent CVD events, ARIC, 1990 - 2011

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Beta index [a]	Quartile Range	2.83 - 8.17	8.18 - 10.28	10.29 - 13.05	13.06 - 44.49	
	N at risk	2459	2447	2398	2353	
	No. events	40	79	84	95	
	Incidence rate, 1000 person-years [b,c]	0.87 (0.64, 1.19)	1.77 (1.42, 2.20)	1.96 (1.58, 2.43)	2.33 (1.91, 2.85)	
	Model 1 HR (95% CI) [c]	1	1.76 (1.20, 2.58)	1.76 (1.20, 2.59)	1.89 (1.28, 2.78)	0.001
	Model 2 HR (95% CI) [d]	1	1.77 (1.19, 2.64)	1.77 (1.19, 2.65)	1.84 (1.23, 2.77)	0.003

CI, confidence interval; HR, hazard ratio

[a] Higher level of the Beta Index indicates less carotid artery distensibility;

[b] Incidence rate per 1000 person-years.

[c] Model 1: Adjusted for age, sex, race, and ARIC center

[d] Model 2: Adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC visit 2.

Table 3.33 Risk of clinical abdominal aortic aneurysm in relation to quartiles of carotid intima-media thickness (cIMT) and quartiles of Beta Index, ARIC, 1987 - 2011

Exposure variable		HR (95%CI) [a,b]				P for trend
	Mutual adjustment	Q1	Q2	Q3	Q4	
cIMT	Not adjusted for Beta Index	1	1.11 (0.80, 1.54)	1.15 (0.84, 1.59)	1.55 (1.13, 2.11)	0.006
	Adjusted for Beta Index quartile	1	1.10 (0.73, 1.67)	1.38 (0.93, 2.04)	1.46 (1.00, 2.14)	0.05
Beta Index	Not adjusted for cIMT	1	1.61 (1.12, 2.31)	1.62 (1.12, 2.33)	1.68 (1.16, 2.43)	0.006
	Adjusted for cIMT quartile	1	1.62 (1.12, 2.33)	1.58 (1.09, 2.30)	1.64 (1.12, 2.39)	0.01

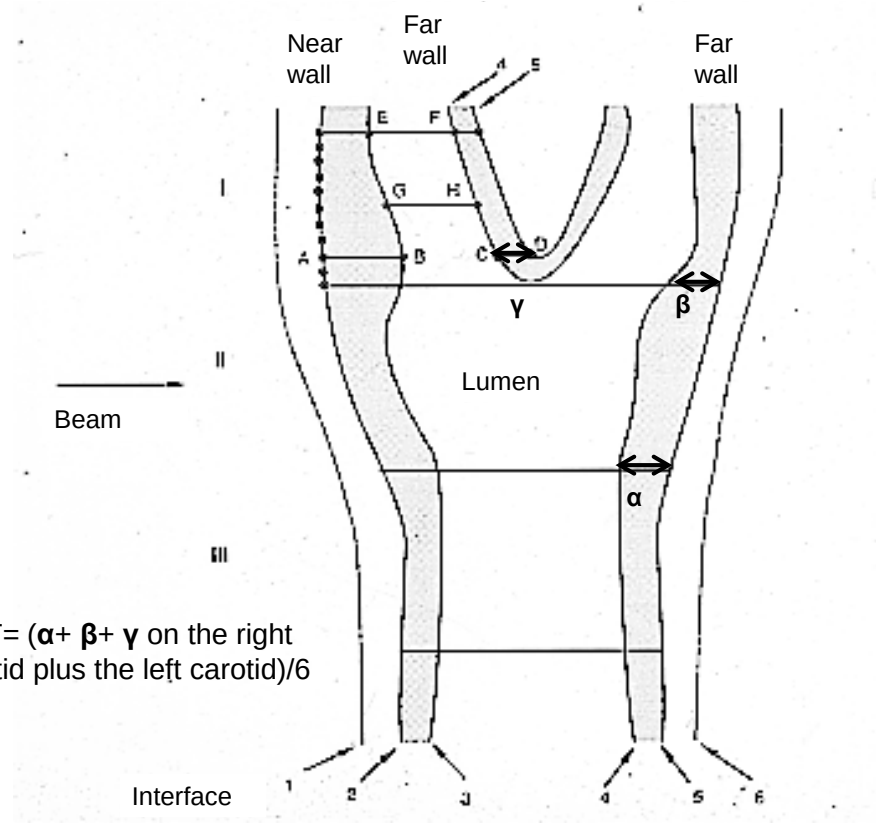
HR: hazard ratio.

[a] For cIMT as the exposure variable, the model also adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 1;

[b] For Beta Index as the exposure variable, the model also adjusted for age, sex, race, ARIC center, height, smoking status, pack-years of smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid medications, systolic blood pressure, use of antihypertensive medications, and diabetes at ARIC Visit 2.

Figure 3.1 Locations of carotid artery B-Mode ultrasound measurements in ARIC.

Schematic Overview of Carotid Artery B-Mode Ultrasound Measurements:



cIMT= (**α**+ **β**+ **γ** on the right carotid plus the left carotid)/6

Figure 3.2 Restricted cubic spline for the natural and log scaled hazard ratio (95% CI) of incident clinical abdominal aortic aneurysm by carotid intima-media thickness (cIMT; in mm) (remove the highest and lowest 1% of cIMT)

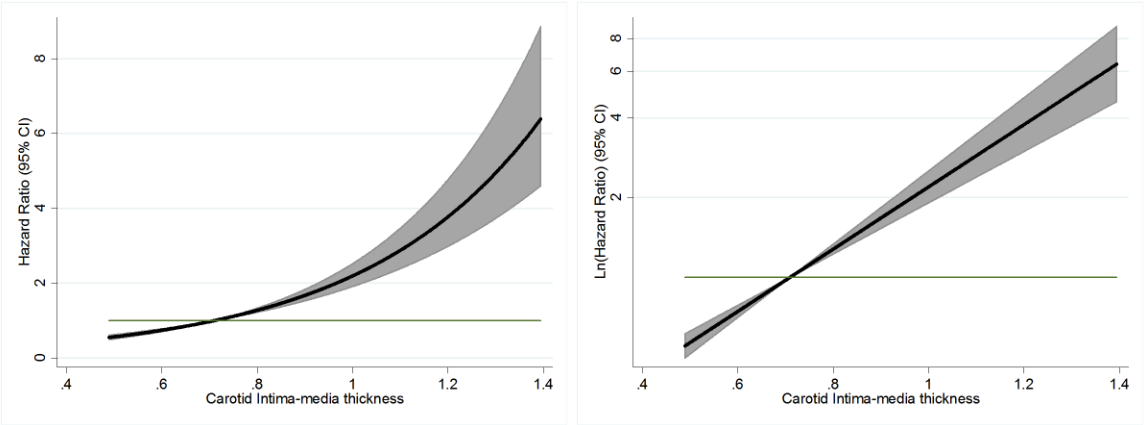


Figure 3.3 Schoenfeld residuals for carotid intima-media thickness (cIMT) over follow-up time

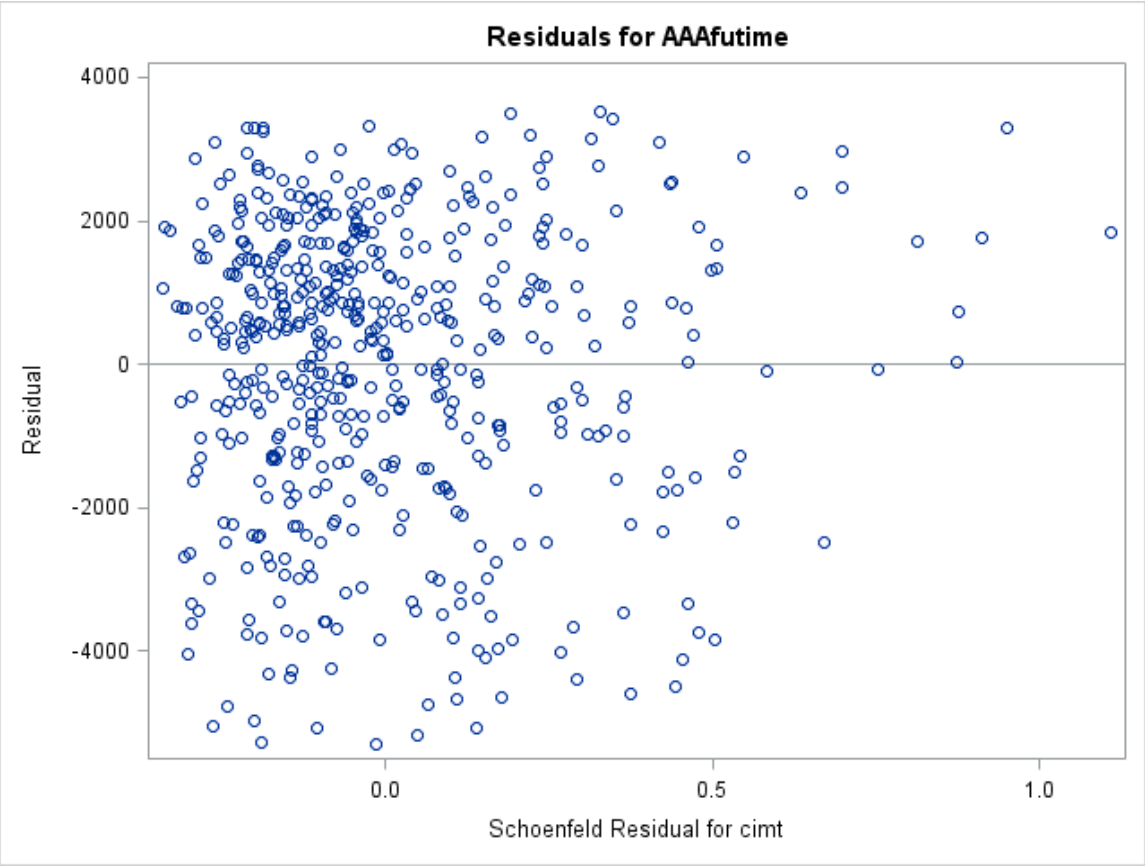


Figure 3.4 Schoenfeld residuals for carotid atherosclerotic plaque over follow-up time

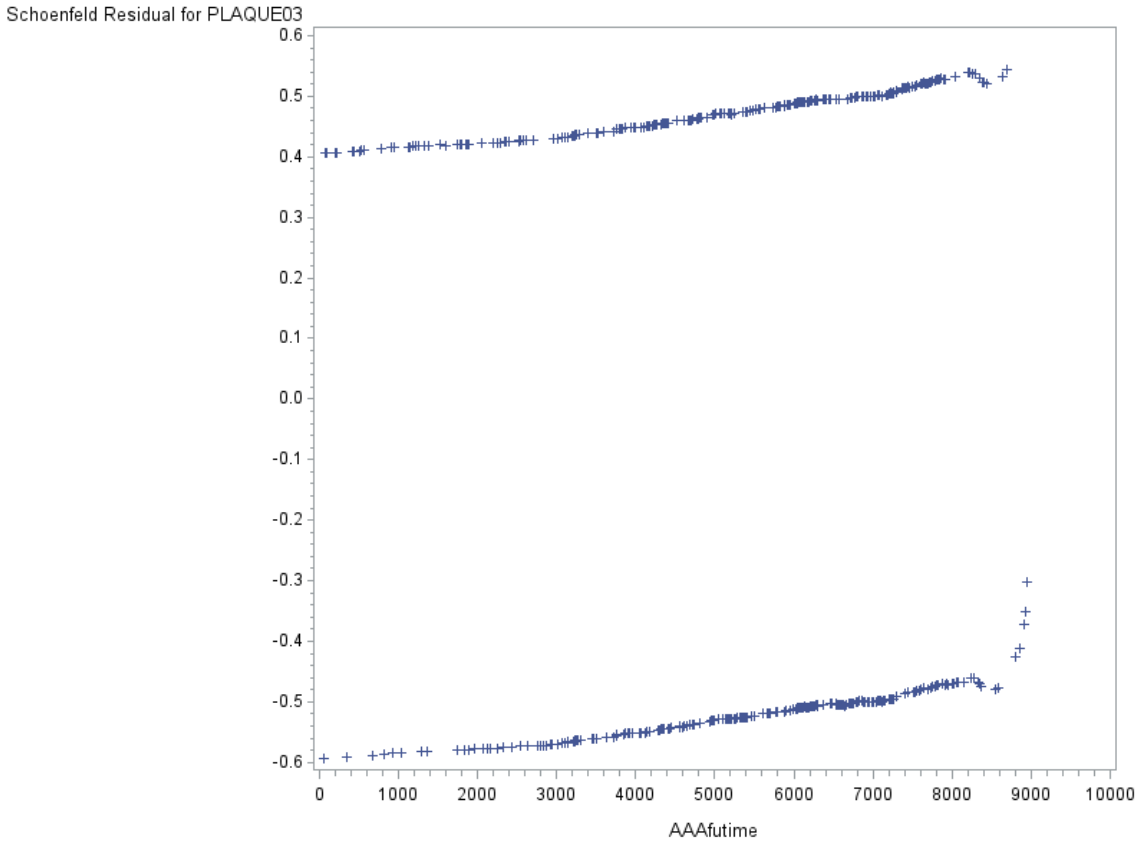


Figure 3.5 Kaplan Meier curves for abdominal aortic aneurysm (AAA) free probability by quartiles of carotid intima-media thickness (cIMT) in ARIC. The data for cIMT were based on the follow-up during 1987 - 2011. The number at risk by the exposure quartile and follow-up year (in 5-year interval) is shown below the graphs.

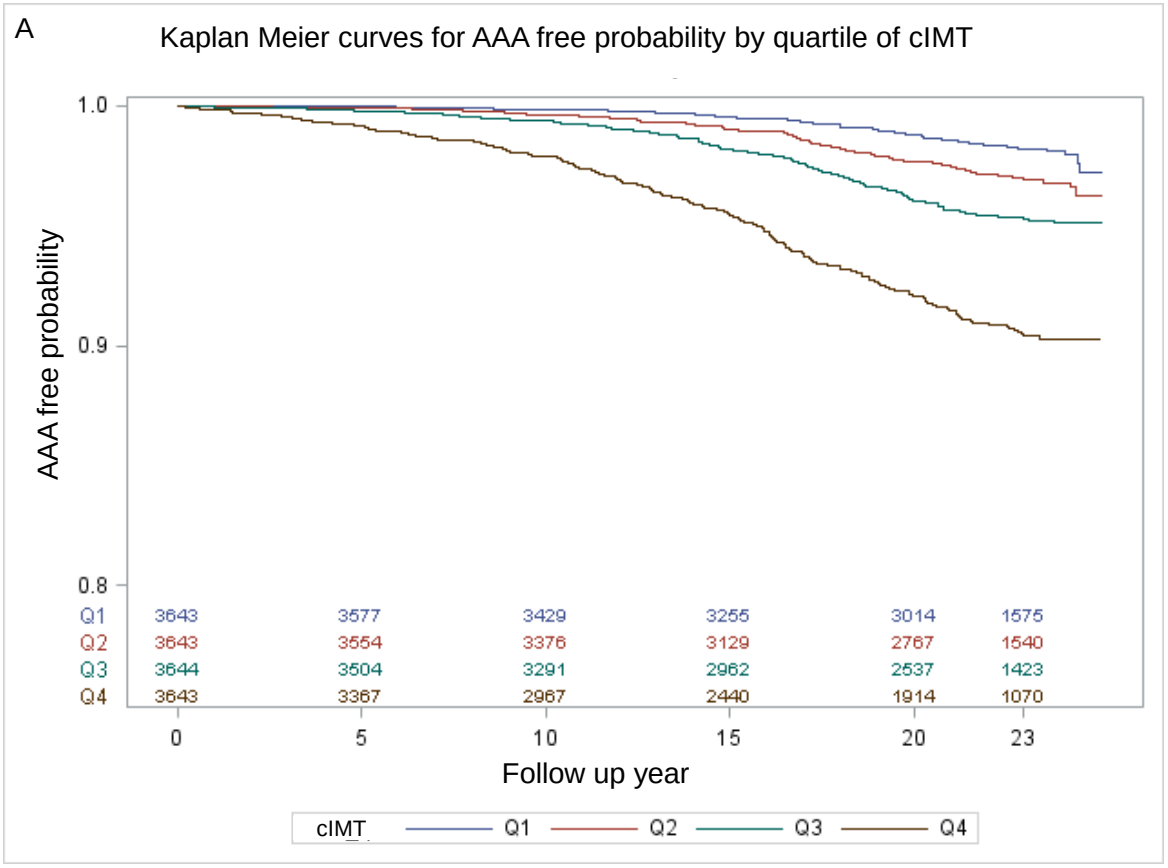


Figure 3.6 Restricted cubic spline for the natural and log scaled hazard ratio (95% CI) of incident clinical abdominal aortic aneurysm by Beta Index (remove the highest and lowest 1% of Beta Index)

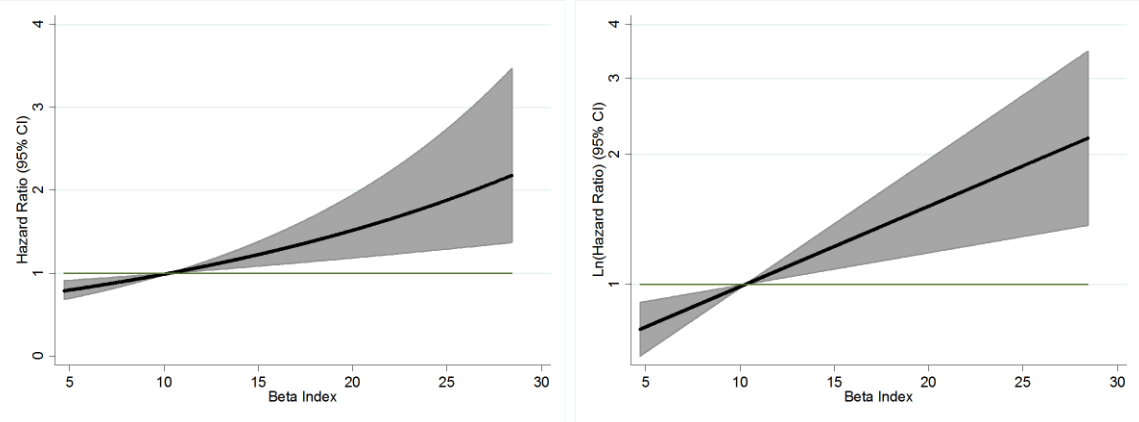


Figure 3.7 Schoenfeld residuals for Beta Index over follow-up time

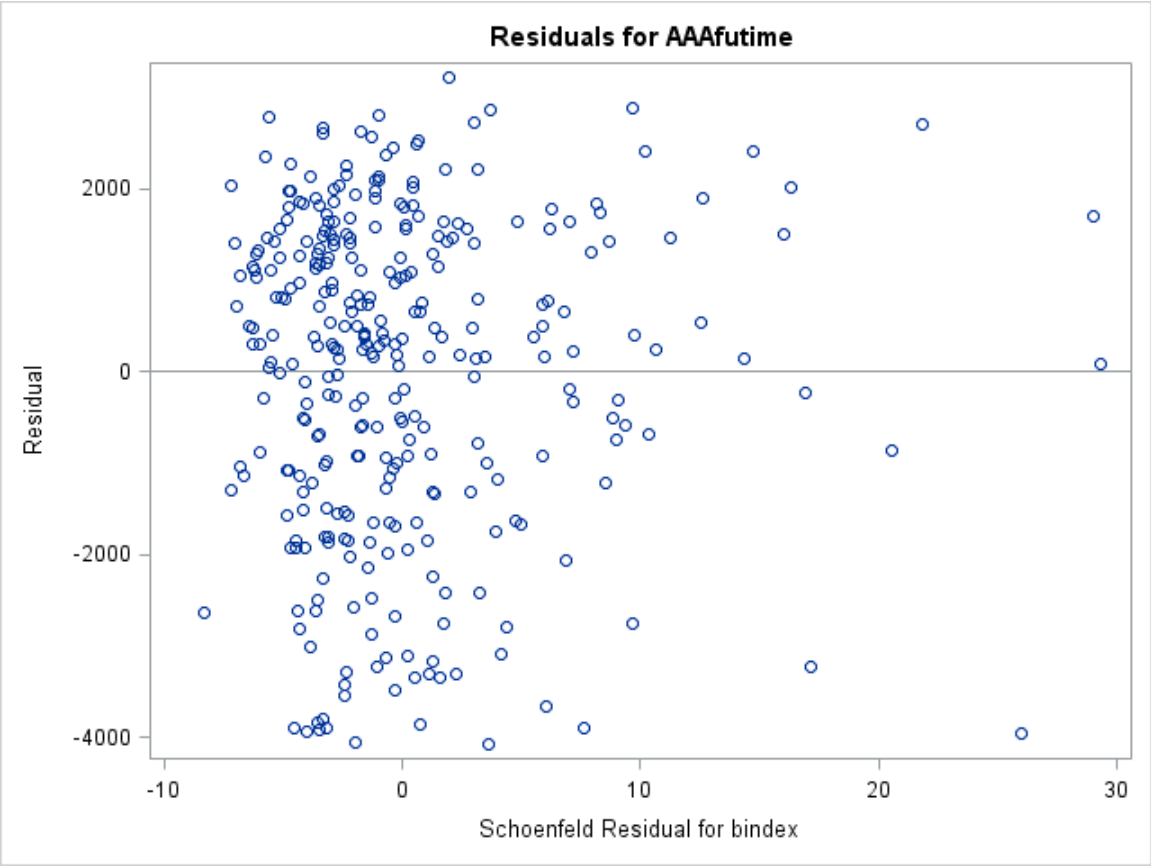
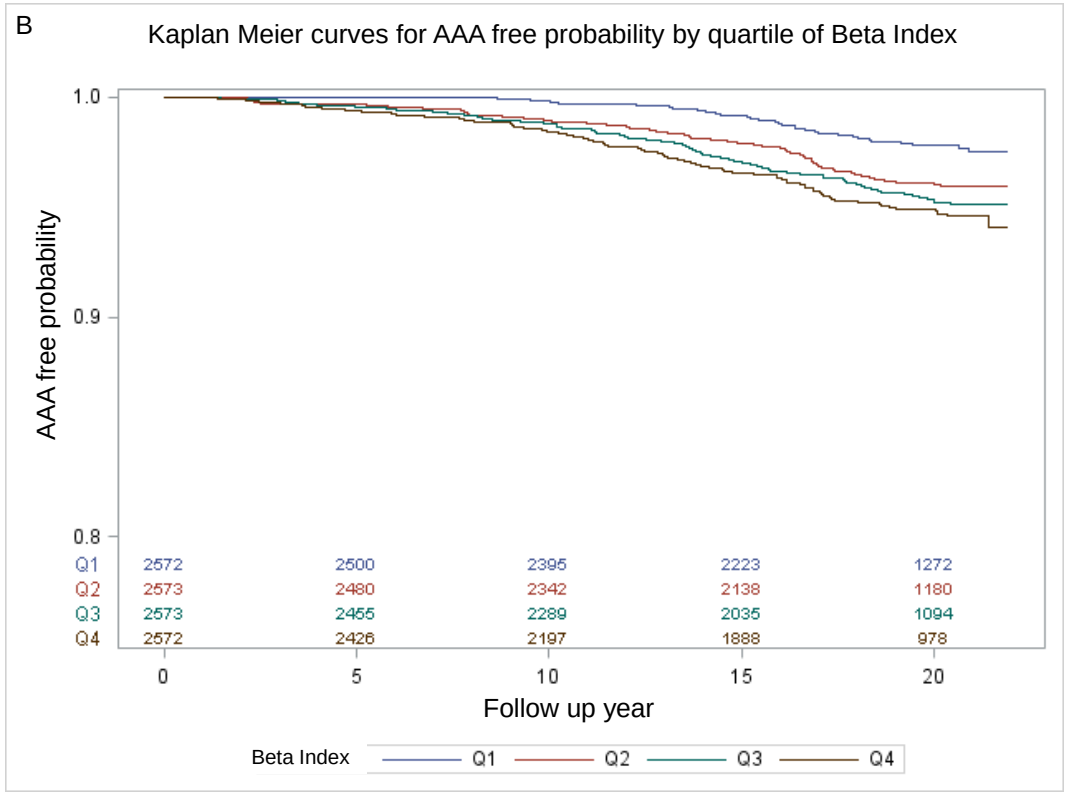


Figure 3.8 Kaplan Meier curves for abdominal aortic aneurysm (AAA) free probability by quartiles of Beta Index in ARIC. The data for Beta Index were based on the follow-up during 1990 - 2011. The number at risk by the exposure quartile and follow-up year (in 5-year interval) is shown below the graphs.



Chapter 4. Manuscript 2: Correlates of infrarenal aortic diameter in a population sample without aneurysms: The Atherosclerosis Risk in Communities (ARIC) Study

4.1 Introduction

An abdominal aortic aneurysm (AAA) is defined using a threshold of aortic diameter. Although there is no consensus for defining AAA,[16,27] some organizations, such as The Society for Vascular Surgery and the International Society for Cardiovascular Surgery, have recommended that AAA be defined as an infrarenal aortic diameter (IAD) 50% greater than the population means reported in the literature.[43] Most experts advocate the use of IAD ≥ 3 cm,[16,28-36,82] a cutpoint more than two standard deviations above the average maximum IAD in the general population.[38] Although a 3 cm cutpoint has been useful for clinical management of AAAs, the biological and pathological evidence for this being the optimal cutpoint is limited.[16,27] For example, autopsy studies have demonstrated ruptures in patients with IAD < 3 cm.[41,42] Furthermore, prospective cohort studies conducted in the US, Europe, and Australia have shown that, compared to an IAD of 2.1-2.3 cm, IADs of 2.4-2.6 cm, and 2.7-2.9 cm were associated with 2.4 and 4.2 fold risk of future AAA, 1.2 and 1.3 fold risk of all-cause mortality, 1.2 and 1.8 fold risk of cardiovascular disease mortality.[36,44-46] The findings from these studies suggest that an IAD above 2.1-2.3 may indicate a pre-AAA stage carrying increased risk for AAA and other life-threatening cardiovascular diseases.

Advanced age, male sex, white race, greater height, obesity, smoking, hypertension, dyslipidemia and absence of diabetes are risk factors for clinically-defined AAA.[48,49,52,149] Of these, male sex, white race, greater height, obesity, smoking, and dyslipidemia are also risk factors for asymptomatic AAA detected by ultrasound exam.[47,50,52,149] If any of these risk factors are associated with an elevated IAD among persons without an AAA, such evidence may help to improve risk stratification and to refine AAA primary prevention strategies. However, the associations of risk factors with an increased, non-aneurysmal IAD have not been extensively examined in population-based studies.[82] Thus, we explored the association between antecedent AAA risk factors and increased non-aneurysmal IAD in a population-based sample.

4.2 Methods

4.2.1 Study population

The Atherosclerosis Risk in Communities (ARIC) Study is a community-based, cohort study conducted in four communities in the US: Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and selected suburbs of Minneapolis, Minnesota.[115] ARIC recruited 15,792 participants 45 - 64 years of age in 1987-89 (Visit 1, baseline); conducted follow-up visits in 1990-92 (Visit 2); 1993-95 (Visit 3); 1996-98 (Visit 4); 2011-13 (Visit 5); and 2016-17 (Visit 6). A seventh visit is underway. Institutional review boards at each study site approved the study, and written informed consent was obtained from all ARIC participants at each study visit.

There were 5,913 participants who had an abdominal ultrasound screening in ARIC Visit 5. We excluded participants whose race was not white or African American (N = 38); those with an asymptomatic AAA detected by the ultrasound exam (maximum IAD ≥ 3 cm, N = 75); unusable IAD in the ultrasound exam (N = 85); uncertain status of AAA (N = 3); and those with clinical AAA identified by hospital discharge codes, death codes, and Medicare outpatient claims prior to the Visit 5 exam (N = 92).[25] After these exclusions, data from 5,620 participants were included in the analysis.

4.2.2 Measurement of abdominal aortic size by ultrasound exam

Details on the abdominal ultrasound scanning in ARIC Visit 5 have been reported elsewhere.[51,52] Briefly, certified cardiac ultrasonographers obtained images with a Philips iE33 high-resolution duplex scanner using a Philips C5-1 transducer in each ARIC field center. Transverse images of anterior-posterior and transverse diameters were recorded at the proximal aorta just below the superior mesenteric artery, the proximal infrarenal aorta 2 cm below the renal arteries, and the distal infrarenal aorta 1 cm above the bifurcation. The ultrasonographers recorded maximal IAD if the maximal diameters could be determined based on the above three measures; otherwise they obtained and used an additional transverse image at the point of maximal IAD. To ensure quality of ultrasound scanning, physicians experienced in reading ultrasound images over-read all images that the sonographers judged had IAD > 2.8 cm or probable pathology, and a 5% random sample of the normal images. We defined

an ultrasound-detected AAA based on maximum IAD measurement ≥ 3 cm,[23] and excluded them from this analysis. Since the physician over-read values were more accurate, we used over-read diameters when available in the analysis. In participants without an AAA, the correlation coefficient for the readings of maximum IADs made between the physicians and sonographers was 0.86 ($P < 0.001$), and the concordance between the readings by physicians and sonographers in classifying an elevated IAD (ranked into the highest IAD quartile) was 91.5%.

4.2.3 Measurement of risk factors

The present study included risk factors collected through ARIC Visit 5. ARIC obtained information on demographic variables, medical history, and traditional cardiovascular risk factors at each visit.[115] Standardized anthropometric measurements of weight, height, and waist circumference were obtained on all participants. Weight was measured to the nearest pound with the participants wearing a scrub suit and no shoes. Height was measured to the nearest centimeter with the participants wearing a scrub suit and no shoes. Body mass index was defined as body weight in kilograms divided by height in meters squared. Waist circumference was measured to the nearest centimeter (cm) at the waist (umbilical level). Participants reported smoking status, the length of smoking history, and the number of cigarettes smoked, and we calculated pack-years of smoking by multiplying the number of years smoked by the mean number of cigarettes per day divided by 20.[126] ARIC collected information on use

of medications from the medication bottles brought to each visit, and measured systolic and diastolic blood pressure three times each in Visits 1 - 3, and twice each in Visits 4 - 5 using random zero sphygmomanometers on the right arm of seated participants after a 5-minute rest period. We used the mean of the last two measurements in Visits 1 - 3 and mean of the two measurements in Visits 4 - 5, in the analysis. Prevalent hypertension was defined as mean systolic pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg or use of antihypertensive medications. Using stored blood specimens from each visit, the ARIC laboratory measured plasma total cholesterol and triglycerides by enzymatic methods, HDL cholesterol after dextran-magnesium precipitation,[134] and calculated LDL cholesterol for those with plasma triglyceride levels ≤ 400 mg/dL by Friedewald methods.[132] Serum or plasma glucose was assessed by the hexokinase method or glucose-6-phosphate dehydrogenase method, depending on the visit.[144] We defined prevalent diabetes mellitus as a fasting glucose ≥ 126 mg/dL, a nonfasting glucose ≥ 200 mg/dL, and/or self-reported physician diagnosis of or treatment for diabetes.

4.2.4 Statistical Analysis

Since most cardiovascular risk variables (except for race and sex) changed over time, we applied the following strategies to assess long-term exposures from middle age (baseline in 1987-89) to the latest visit available for a participant (maximum: Visit 5 in 2013). For waist circumference, body mass index, total cholesterol, HDL cholesterol, and LDL cholesterol, we calculated the

cumulative risk factor as the weighted average across Visit 1- Visit 5, weighted by the number of years between each examination.[159] For example, the cumulative HDL value was calculated by summing the product of the average HDL concentration from two consecutive examinations and the corresponding time interval (in years) between the two examinations, divided by the time interval (in years) between Visit 1 and Visit 5. We coded the use of lipid-lowering medication as 'ever positive/yes' in our analysis if it was categorized as positive/yes in at least one visit; otherwise it was coded as 'never positive.' Diabetes and hypertension were categorized as never, short-term (incident cases occurring 1998 to 2011-13), intermediate-term (incident cases occurring 1987-89 to 1996-98), and long-term (prevalent cases at 1987-89). We used age and pack-years of smoking at Visit 5 directly because these two variables reflect cumulative values. Height at Visit 1 was used in the analysis. For both continuous and categorical variables, we imputed a missing value at a given visit using the value in the previous examination. The proportions of the sample with imputed values varied from 9.2% to 25.2%, depending on the variable.

We defined the outcome of this study, an elevated IAD, as being in the highest quartile of the IAD distribution (i.e., IAD ≥ 2.2 cm) without an AAA. Participants whose IAD was under 2.2 cm were analyzed as the reference group. Although AAA risk has not been shown to be absent at an IAD as low as 1.8 cm, AAA risk increases exponentially as IAD increases beyond 2.2 cm.[45] Thus, 2.2 cm was chosen *a priori* as the cutpoint for the present analysis as it indicates

clearly elevated risk of clinical AAA. As previously described, we used inverse probability weighting to account for attrition due to loss to follow-up and death prior to the 2011-13 ARIC Visit 5.[148] The weights were calculated based on the product of the probability of being alive in 2011-13 and the probability of having an abdominal ultrasound, conditional on being alive.[25] Odds ratios (ORs) and 95% confidence intervals (CIs) of elevated IAD were obtained for each cumulative risk factor estimate from inverse probability of attrition weighted general estimating equation models. For each continuous risk factor, we calculated an OR for each quintile of the variable, with the lowest quintile as the reference group. For diabetes and hypertension, we calculate an OR associated with each category of the variable, with the “never” group as the reference group. We tested trends in ORs across quantiles by analyzing the quantile value as an ordinal variable. The basic models adjusted for baseline age, sex, race, and field center. The fully-adjusted model additionally and simultaneously adjusted for all potential risk factors including height, waist circumference, total cholesterol, HDL cholesterol, smoking pack-year, diabetes, and hypertension. Models of LDL cholesterol did not adjust for total cholesterol. We included the use of lipid-lowering medications as a covariate in the multivariate adjustment model because use of lipid-lowering medications altered lipid profiles[160] and might be associated with reduced AAA risk.[112] A sensitivity analysis was conducted by replacing height by body mass index in the fully-adjusted model. Since body size differs remarkably by sex, we examined the association of body size (height and waist circumference) with

elevated IAD stratified on sex in a secondary data analysis. All analyses were performed using SAS (Version 9.4, SAS Institute Inc., Cary, NC, USA)

4.3 Results

4.3.1 Sample characteristics

The final sample included 2,268 (40.4%) men and 3,352 (59.6%) women, and 4,374 (77.8%) whites and 1,246 (22.2%) blacks. The mean age was 51.7 years (SD 5.0) at baseline and 75.4 (SD 5.1) at Visit 5 when the ultrasound exam was performed. On average, participants in the highest quartile of IAD compared to the rest were more often male and blacks, were taller, had greater body mass index and larger waist circumference, more pack-years of smoking, and lower concentrations of total cholesterol, and HDL cholesterol (P for difference < 0.001 for all; **Table 4.1)**.

4.3.2 Associations of elevated IADs with AAA risk factors

Table 4.2 shows data on associations of elevated IADs with AAA risk factors. In the basic models (adjusted for age, sex, race, and field center), male sex, height, waist circumference, and smoking pack-years were positively associated with elevated IADs while HDL cholesterol, diabetes, and hypertension were inversely associated with an elevated IAD (P < 0.05). Participants in the highest quintiles of height, waist circumference, cigarette pack-years, and HDL cholesterol had 2.34 (95% CI: 1.65, 3.32) fold higher, 1.61 (95% CI: 1.23, 2.09) fold higher, 1.65 (95% CI: 1.29, 2.11) fold higher, and 0.74 (95% CI: 0.56, 0.98)

fold odds of having an elevated IAD, respectively, compared to those in the lowest quintiles. Men had 4.15 (95% CI: 3.56, 4.84; P<0.001) fold higher odds of having elevated IAD than women. Participants with long-term diabetes and hypertension had 0.70 (95% CI: 0.52, 0.93) and 0.81 (95% CI: 0.68, 0.98) lower odds of having an elevated IAD, respectively. Age, race, total cholesterol, and LDL cholesterol were not significantly associated with IAD.

With mutual adjustment for all covariates plus lipid-lowering medications in the fully-adjusted model, all of the significant associations observed in the basic adjustment models remained, except that HDL cholesterol and hypertension were no longer associated with elevated IADs. Height, waist circumstance and smoking pack-years were positively associated with elevated IADs [ORs (95% CI) for the highest vs. lowest quintiles of the risk factor: 1.93 (1.36, 2.75), 1.67 (1.28, 2.19) and 1.62 (1.26, 2.08), respectively; P for trend: <0.001 for all). The dose-response associations of height, waist circumstance and smoking pack-years with elevated IAD are further depicted in **Figures 4.1 A- 4.1 C**. Men had 2.50 (95% CI: 1.90, 3.28; P for difference < 0.001) times higher odds of having elevated IADs than females. Participants with long-term diabetes had 0.52 (95% CI: 0.35, 0.77; P for trend: 0.004) times lower odds of having an elevated IAD than participants without diabetes.

The sensitivity analysis replacing height by body mass index in the fully-adjusted model showed results similar to the primary analysis. The association between waist circumference and elevated IADs was attenuated, but in the same

direction as in the primary analysis **(Table 4.3)**. BMI was positively associated with greater IAD in the basic model, but the positive association was no longer significant in the fully-adjusted model (**Table 4.3**).

There was no significant interaction for waist circumference and height by sex in the association with elevated IAD either in the basic model or in the fully-adjusted model (P for interaction > 0.20 for all). The secondary analyses conducted in each sex group showed height and waist circumference positively associated with IAD both in men and women (**Table 4.4**).

4.4 Discussion

In this population-based prospective study, male sex, greater height, greater pack-years cigarette smoking, and larger waist circumference were independently associated with elevated IAD in persons without an AAA (i.e. maximum IAD ≥ 3.0 cm). Previous studies have demonstrated that an elevated IAD (2.3 - 3.0 cm) within the normal range was positively associated with the risk of AAA and cardiovascular morbidity and mortality.[36,44-46] Our study provides data to improve the understanding of AAA etiology by extending risk factor information to the pre-AAA stage. The identification of overlapping risk factors between AAA and less elevated IAD suggests that the pathophysiological mechanisms that lead to AAA development likely start or become activated during the pre-AAA stage. Thus, primary prevention efforts that focus on these risk factors at the pre-AAA stage may be an effective strategy in reducing AAA occurrence, progression, and cardiovascular mortality, a hypothesis that could be tested in clinical trials.

Our results regarding height, measures of adiposity, male sex, and smoking were consistent with most previous cross-sectional studies conducted in clinical settings.[77-80] Among population-based studies, Lederle and colleagues found that male sex, greater height, and larger waist circumference were associated with greater IAD in a cross-sectional survey among men and women aged 55-70 years who had no AAA history and IAD < 3 cm.[82] Similar results regarding waist circumference and IAD were observed in a cross-sectional analysis in the Framingham Heart Study.[81] Another non-concurrent cross-sectional analysis using data from Tromso, Norway (mean age: 59 years) showed that male sex and cigarette smoking were positively associated with IAD measured 5.4-7.2 years later.[55] However, both the Framingham Heart and the Tromso studies did not conduct a separate analysis among subjects without AAA.[55,81] In comparison, our sample consists of community-dwelling black and white participants free of AAA, and information on AAA risk factors was cumulated over multiple visits during a follow-up of more than 20 years. Therefore, our study provides information in addition to what has already been reported. Our observation along with previous findings suggests a role of male sex, greater height, greater adiposity, and smoking in the early stages of AAA development.

Given the strong correlation between male sex and IAD, the role of sex hormones in the development of AAA is of interest. However, there is no clear evidence that male sex hormones are positively associated with AAA nor female

hormones inversely related to AAA. Yet, data from animal studies suggested that male sex hormones promote AAA,[161,162] and a cross-sectional study of older men showed that circulating free testosterone was inversely associated with AAA.[163] In a prospective cohort study of women, hormone replacement therapy of > 5 years was associated with decreased risk of AAA (OR (95% CI) = 0.52 (0.34, 0.78)),[48] but this association was not observed in another cohort study conducted in an integrated health-care delivery system.[49] On the other hand, hormone replacement therapy may trigger adverse thrombotic and proinflammatory outcomes.[164] To our knowledge, there is no human study examining the role of endogenous estrogen in AAA. Men had larger IAD than women after accounting for body size (height and waist circumference) in the fully-adjusted model, indicating that the excess risk of men over women is not attributable to differences in body size. Further studies are required to clarify why men have higher IADs.

The pathophysiological mechanisms underlying the associations of greater height, larger waist circumference, and smoking with elevated IAD are not well understood. The positive associations of height and waist circumference with elevated IAD are unlikely to be confounded by sex because we adjusted for sex in both basic and fully-adjusted models. Also, our sex-specific sensitivity analysis suggested height and waist circumference were positively associated with elevated IAD in both men and women. Animal studies have shown that smoking is involved in early stages of aneurysmal dilation of the aorta, including

accelerated elastin degradation,[165,166] and this might be mediated through altered peripheral blood leukocyte response to aortic injury, activation of matrix metalloproteinases and inflammation, and apoptosis of smooth muscle cells.[167-169]

Regarding the negative association between diabetes and elevated IAD, both an age- and sex-adjusted analysis from the Tromso study[55] and a clinical-based study that included AAAs and non-AAAs[78] reported the same direction of association between prevalent diabetes and IAD. In contrast, another clinical-based study did not report any relation between newly-diagnosed diabetes and IAD.[77] Evidence indicates that long-term diabetes rather than short-term diabetes may matter in relation to IAD, which is in line with our results. The diabetes- IAD relationship might be confounded by indication, because some diabetic medications such as metformin[170,171] and thiazolidinediones,[172] including rosiglitazone,[173,174] may inhibit the development of AAA. However, we were unable to examine the effects of diabetes medication use. Alternatively, the negative association between diabetes and IAD might be attributed to hyperglycemia and the advanced glycation products associated with diabetes. Hyperglycemia has been associated with a reduction in proteolysis of matrix in the arterial wall,[175] decreased aortic wall stress,[103,104] and increased collagen synthesis.[173,176,177] The advanced glycation products associated with diabetes may increase smooth muscle cell proliferation and induce cross-linking of collagen lattices in the media of the aorta, thereby reducing dilation.[178,179] More

evidence is needed to clarify the causal relationship between diabetes and reduced IAD.

In the Framingham Heart Study, HDL cholesterol was inversely correlated with IAD as well as other measures of aortic diameters in sex-specific, age-adjusted univariate analysis.[81] Our result in the basic model, that HDL cholesterol was inversely associated with elevated IAD, was consistent with the Framingham results.[81] However, our fully-adjusted model suggested the relationship no longer existed. This suggests that the effects of HDL on elevated IAD may be confounded by other factors included in the fully-adjusted model such as body size, hypertension, diabetes, and smoking.

There is a perception that IAD increases with age.[82] However, our study showed no significant association between age and elevated IAD after adjustment for potential confounding variables. Advanced age was associated with elevated IADs in previous studies; however, these studies either were conducted in clinical settings[77,78] or in populations younger than ours (mean age 59 years vs 75 years at ultrasound measurement).[55,82] In comparison, several population-based studies not excluding AAA showed that median IAD remained stable after 55 years of age (mean ages range from 61.1 to 72.5 years).[46,83-85] Thus, the age-IAD relation is unclear and further studies are warranted to address this issue.

The strengths of our study include high quality measurements of risk factors and outcomes, a large sample size, and our use of cumulative long-term

exposure for the AAA risk factors. Nonetheless, this study is subject to some limitations. As in other observational studies, residual confounding cannot be eliminated. Measurement errors may have occurred in the aortic diameter data. However, we observed a high correlation between the readings made by the ultrasonographers and physicians; we also used a binary outcome (the highest quartile of IAD vs. the rest) to minimize the impact of outliers and measurement error. Finally, the use of a carry forward method for imputing missing values may misclassify risk factor levels across multiple time points for some participants.

In summary, we identified that male sex, greater pack-years of smoking, greater height, larger waist circumference, and absence of diabetes were associated with elevated IADs in persons without an AAA in this large population-based sample. Our findings enhance understanding of the risk factor profile for the pre-AAA stage and have the potential to improve risk stratification and the prevention of AAA.

4.5 Tables

Table 4.1 Baseline characteristics (mean (SD) or N (%)) according to maximal infrarenal aortic diameter (IAD) in ARIC participants without abdominal aortic aneurysms (N = 5620)

Characteristic	Maximum IAD		P value [b]
	Lower three quartiles (< 2.2 cm)	Highest quartile (≥ 2.2 cm)	
Age at V1, years	51.7 (5.0)	51.9 (5.1)	0.33
Age at V5, years	75.4 (5.1)	75.5 (5.1)	0.96
Male (%)	29.2	64.5	<0.001
White (%)	80.0	73.1	<0.001
Height at V1, cm	166.4 (8.5)	172.8 (9.1)	<0.001
Waist circumference, cm	98.1 (12.5)	101.5 (12.1)	<0.001
Body mass index, kg/m^2	28.0 (5.0)	28.8 (4.8)	<0.001
Smoking, pack-years [c]	23.9 (20.6)	27.0 (22.9)	<0.001
Diabetes (%)	28.7	29.6	0.51

Hypertension (%)	75.9	74.4	0.20
Total cholesterol, mg/dL	198.8 (28.6)	192.8 (29.8)	<0.001
LDL cholesterol, mg/dL	119.5 (25.0)	118.6 (26.2)	0.25
HDL cholesterol, mg/dL	53.7 (14.6)	48.9 (13.6)	<0.001
Use of lipid lowering medication (%)	57.9	56.8	0.46

HDL, high-density lipoprotein; LDL, low-density lipoprotein

[a] Values of continuous risk factors (except for age and height which were from Visit 1) were cumulative averages among five visits, and values of categorical risk factors were ever/never across five visits.

[b] P value from Student's t test or chi-square test.

[c] Among ever smokers only.

Table 4.2 Adjusted odds ratios and confidence intervals for the associations between risk factors and greater infrarenal aortic diameter (≥ 2.2 cm).

	N at risk	N events [c]	Model 1 [d]	Model 2 [e]
Age at V5, year				
Q1 (66, 71)	1543	469	1	1
Q2 (72, 73)	829	273	1.29 (1.03, 1.62)	1.33 (1.06, 1.67)
Q3 (74, 76)	1072	334	1.15 (0.94, 1.42)	1.16 (0.94, 1.43)
Q4 (77, 80)	1145	368	1.19 (0.93, 1.51)	1.27 (1.01, 1.59)
Q5 (81, 90)	1031	330	1.08 (0.84. 1.37)	1.22 (0.96, 1.55)
P for trend			0.55	0.22
Male				
No	3352	630	1	1
Yes	2268	1144	4.15 (3.56, 4.84)	2.50 (1.90, 3.28)
P for difference			<0.001	<0.001

White race				
No	1246	477	1	1
Yes	4374	1,297	0.84 (0.47, 1.47)	0.82 (0.48, 1.43)
P for difference			0.54	0.37
Height at V1, cm				
Q1 (144, 160)	1191	182	1	1
Q2 (161, 165)	1181	233	1.03 (0.80, 1.32)	0.96 (0.74, 1.23)
Q3 (166, 170)	1065	299	1.50 (1.12, 2.03)	1.35 (1.01, 1.80)
Q4 (171, 177)	1134	467	1.48 (1.07, 2.05)	1.36 (0.98, 1.88)
Q5 (178, 199)	1047	591	2.34 (1.65, 3.32)	1.93 (1.36, 2.75)
P for trend			<0.001	<0.001
Waist circumference, cm [a]				
Q1 (63.4, 88.8)	1128	230	1	1
Q2 (88.9, 95.4)	1121	328	0.97 (0.75, 1.24)	1.04 (0.81, 1.33)

Q3 (95.5, 101.6)	1123	352	0.95 (0.73, 1.23)	0.98 (0.75, 1.29)
Q4 (101.7, 109.0)	1126	437	1.40 (1.09, 1.79)	1.45 (1.11, 1.88)
Q5 (109.1, 149.7)	1119	424	1.61 (1.23, 2.09)	1.67 (1.28, 2.19)
P for trend			<0.001	<0.001
Total cholesterol, mg/dL [a]				
Q1 (96, 172)	1122	448	1	1
Q2 (173, 188)	1129	405	0.97 (0.77, 1.21)	0.95 (0.76, 1.19)
Q3 (189, 202)	1117	324	0.91 (0.70, 1.17)	0.93 (0.73, 1.19)
Q4 (203, 220)	1123	297	0.77 (0.61, 0.98)	0.80 (0.63, 1.02)
Q5 (221, 378)	1121	298	0.86 (0.67, 1.10)	0.92 (0.71, 1.18)
P for trend			0.07	0.25
LDL cholesterol, mg/dL [a]				
Q1 (17.6, 39.7)	1118	380	1	1
Q2 (39.8, 46.5)	1119	365	0.90 (0.72, 1.13)	0.87 (0.70, 1.10)

Q3 (46.6, 53.6)	1119	334	0.88 (0.70, 1.12)	0.86 (0.67, 1.09)
Q4 (53.7, 63.5)	1119	349	1.02 (0.80, 1.31)	0.97 (0.77, 1.23)
Q5 (63.6, 118.4)	1118	333	0.91 (0.72, 1.16)	0.90 (0.71, 1.15)
P for trend			0.95	0.76
HDL cholesterol, mg/dL [a]				
Q1 (27.6, 99.0)	1122	471	1	1
Q2 (99.1, 112.2)	1123	435	1.02 (0.81, 1.29)	1.05 (0.83, 1.32)
Q3 (112.3, 124.1)	1122	339	0.82 (0.63, 1.07)	0.89 (0.69, 1.15)
Q4 (124.2, 139.1)	1123	281	0.74 (0.58, 0.96)	0.84 (0.64, 1.09)
Q5 (139.2, 291.0)	1122	246	0.74 (0.56, 0.98)	0.89 (0.66, 1.19)
P for trend			0.007	0.24
Pack-years of smoking [a]				
Q1 (0, 0)	2946	744	1	1
Q2 (0.1, 8.5)	654	223	1.30 (1.05, 1.62)	1.32 (1.07, 1.63)

Q3 (8.6, 19.5)	651	238	1.29 (1.05, 1.59)	1.24 (1.01, 1.53)
Q4 (19.6, 36.2)	651	240	1.53 (1.15, 2.03)	1.61 (1.25, 2.08)
Q5 (36.3, 186.0)	652	275	1.65 (1.29, 2.11)	1.62 (1.26, 2.08)
P for trend			<0.001	<0.001
Diabetes [b]				
Never	3990	1249	1	1
Short-term	904	299	1.07 (0.91, 1.26)	1.02 (0.84, 1.25)
Intermediate-term	435	147	0.92 (0.72, 1.19)	0.95 (0.67, 1.34)
Long-term	291	79	0.70 (0.52, 0.93)	0.52 (0.35, 0.77)
P for trend			0.06	0.004
Hypertension [b]				
Never	1381	455	1	1
Short-term	1787	569	0.90 (0.77, 1.06)	0.91 (0.75, 1.10)
Intermediate-term	1143	334	0.80 (0.66, 0.97)	0.73 (0.57, 0.93)

Long-term	1309	416	0.81 (0.68, 0.98)	0.81 (0.65, 1.01)
P for trend			0.01	0.06

HDL, high-density lipoprotein; LDL, low-density lipoprotein; Q, quintile

[a] Values were cumulative averages among five visits, weighted by time interval between the visits.

[b] Disease status was classified as were never, short-term (since 2011 - 13), moderate (since 1990 - 92), and long-term (since 1987 - 89 and earlier).

[c] Events were defined as being in the highest quartile of infrarenal aortic diameters distribution (≥ 2.2 cm).

[d] Adjusted for age, sex, race, and field center.

[e] Adjusted for age at V5, sex, race, field center, height, waist circumference, total cholesterol, HDL cholesterol, lipid-lowering medication use, pack-years of smoking, diabetes, and hypertension; models of LDL cholesterol did not adjust for total cholesterol

Table 4.3 Adjusted odds ratios and confidence intervals for the associations between risk factors and greater infrarenal aortic diameter (≥ 2.2 cm) in the sensitivity analysis.

	N at risk	N Event [c]	Model 1 [d]	Model 2 [e]
Age at V5, year				
Q1 (66, 71)	1543	469	1	1
Q2 (72, 73)	829	273	1.29 (1.03, 1.62)	1.32 (1.05, 1.66)
Q3 (74, 76)	1072	334	1.15 (0.94, 1.42)	1.15 (0.93, 1.42)
Q4 (77, 80)	1145	368	1.19 (0.93, 1.51)	1.26 (1.01, 1.58)
Q5 (81, 90)	1031	330	1.08 (0.84. 1.37)	1.18 (0.93, 1.51)
P for trend			0.55	0.31
Male				
No	3352	630	1	1
Yes	2268	1144	4.15 (3.56, 4.84)	3.68 (3.05, 4.45)
P for difference			<0.001	<0.001

White race				
No	1246	477	1	1
Yes	4374	1297	0.84 (0.47, 1.47)	0.86 (0.50, 1.49)
P for difference			0.54	0.52
Body mass index, kg/m^2				
Q1 (15.7, 24.1)	1123	263	1	1
Q2 (24.2, 26.4)	1124	349	0.91 (0.71, 1.16)	0.95 (0.72, 1.25)
Q3 (26.5, 28.7)	1124	369	0.97 (0.76, 1.24)	0.92 (0.68, 1.26)
Q4 (28.8, 31.8)	1124	385	1.14 (0.89, 1.45)	0.98 (0.69, 1.41)
Q5 (31.9, 56.5)	1123	406	1.62 (1.25, 2.12)	1.31 (0.86, 2.01)
P for trend			<0.001	0.20
Waist circumference, cm [a]				
Q1 (63.4, 88.8)	1128	230	1	1
Q2 (88.9, 95.4)	1121	328	0.97 (0.75, 1.24)	1.08 (0.82, 1.43)

Q3 (95.5, 101.6)	1123	352	0.95 (0.73, 1.23)	1.05 (0.76, 1.45)
Q4 (101.7, 109.0)	1126	437	1.40 (1.09, 1.79)	1.48 (1.04, 2.11)
Q5 (109.1, 149.7)	1119	424	1.61 (1.23, 2.09)	1.49 (0.98, 2.25)
P for trend			<0.001	0.07
Total cholesterol, mg/dL [a]				
Q1 (96, 172)	1122	448	1	1
Q2 (173, 188)	1129	405	0.97 (0.77, 1.21)	0.96 (0.76, 1.20)
Q3 (189, 202)	1117	324	0.91 (0.70, 1.17)	0.95 (0.74, 1.21)
Q4 (203, 220)	1123	297	0.77 (0.61, 0.98)	0.81 (0.64, 1.02)
Q5 (221, 378)	1121	298	0.86 (0.67, 1.10)	0.92 (0.72, 1.18)
P for trend			0.07	0.20
LDL cholesterol, mg/dL [a]				
Q1 (17.6, 39.7)	1118	380	1	1
Q2 (39.8, 46.5)	1119	365	0.90 (0.72, 1.13)	0.90 (0.71, 1.13)

Q3 (46.6, 53.6)	1119	334	0.88 (0.70, 1.12)	0.87 (0.68, 1.10)
Q4 (53.7, 63.5)	1119	349	1.02 (0.80, 1.31)	0.99 (0.78, 1.25)
Q5 (63.6, 118.4)	1118	333	0.91 (0.72, 1.16)	0.92 (0.73, 1.17)
P for trend			0.95	0.75
HDL cholesterol, mg/dL [a]				
Q1 (27.6, 99.0)	1122	471	1	1
Q2 (99.1, 112.2)	1123	435	1.02 (0.81, 1.29)	1.05 (0.83, 1.33)
Q3 (112.3, 124.1)	1122	339	0.82 (0.63, 1.07)	0.90 (0.69, 1.17)
Q4 (124.2, 139.1)	1123	281	0.74 (0.58, 0.96)	0.85 (0.65, 1.11)
Q5 (139.2, 291.0)	1122	246	0.74 (0.56, 0.98)	0.91 (0.68, 1.23)
P for trend			0.007	0.37
Pack-years of smoking [a]				
Q1 (0, 0)	2946	744	1	1
Q2 (0.1, 8.5)	654	223	1.30 (1.05, 1.62)	1.34 (1.08, 1.65)

Q3 (8.6, 19.5)	651	238	1.29 (1.05, 1.59)	1.26 (1.02, 1.55)
Q4 (19.6, 36.2)	651	240	1.53 (1.15, 2.03)	1.60 (1.23, 2.08)
Q5 (36.3, 186.0)	652	275	1.65 (1.29, 2.11)	1.65 (1.29, 2.12)
P for trend			<0.001	<0.001
Diabetes [b]				
Never	3990	1249	1	1
Short-term	904	299	1.07 (0.91, 1.26)	1.01 (0.82, 1.23)
Intermediate-term	435	147	0.92 (0.72, 1.19)	0.93 (0.65, 1.32)
Long-term	291	79	0.70 (0.52, 0.93)	0.51 (0.34, 0.76)
P for trend			0.06	0.003
Hypertension [b]				
Never	1381	455	1	1
Short-term	1787	569	0.90 (0.77, 1.06)	0.89 (0.74, 1.08)
Intermediate-term	1143	334	0.80 (0.66, 0.97)	0.70 (0.55, 0.90)

Long-term	1309	416	0.81 (0.68, 0.98)	0.79 (0.64, 0.99)
P for trend			0.01	0.04

HDL, high-density lipoprotein; LDL, low-density lipoprotein; Q, quintile.

[a] Values were cumulative averages among five visits, weighted by time interval between the visits.

[b] Disease status was classified as were never, short-term (since 2011 - 13), moderate (since 1990 - 92), and long-term. (since 1987 - 89 and earlier).

[c] Events were defined as being in the highest quartile of infrarenal aortic diameters distribution (≥ 2.2 cm).

[d] Adjusted for age, sex, race, and field center.

[e] Adjusted for age at V5, sex, race, field center, body mass index, waist circumference, total cholesterol, HDL cholesterol, lipid-lowering medication use, pack-years of smoking, diabetes, and hypertension; models of LDL cholesterol did not include total cholesterol.

Table 4.4 Adjusted odds ratios and confidence intervals for the associations between risk factors and greater infrarenal aortic diameter (≥ 2.2 cm) by sex.

	N at risk	N events [b]	Model 1 [c]	Model 2 [d]
Male				
Height at V1, cm				
Q1 (157, 171)	491	206	1	1
Q2 (172, 175)	455	208	1.18 (0.86, 1.63)	1.15 (0.84, 1.58)
Q3 (176, 178)	417	199	1.15 (0.83, 1.61)	1.08 (0.78, 1.50)
Q4 (179, 182)	471	268	1.90 (1.39, 2.61)	1.64 (1.20, 2.24)
Q5 (183, 199)	402	246	2.03 (1.47, 2.81)	1.84 (1.32, 2.55)
P for trend			<0.001	<0.001
Waist circumference, cm [a]				
Q1 (71.6, 93.3)	446	206	1	1
Q2 (93.4, 98.3)	451	209	0.94 (0.68, 1.29)	0.97 (0.71, 1.34)

Q3 (98.4, 103.2)	449	214	0.98 (0.72, 1.33)	1.03 (0.75, 1.41)
Q4 (103.3, 109.5)	443	241	1.48 (1.09, 2.00)	1.44 (1.04, 1.99)
Q5 (109.6, 149.7)	447	256	1.52 (1.09, 2.10)	1.68 (1.18, 2.38)
P for trend			<0.001	<0.001
Female				
Height at V1, cm				
Q1 (144, 158)	798	101	1	1
Q2 (159, 161)	585	108	1.53 (1.07, 2.18)	1.48 (1.04, 2.12)
Q3 (162, 164)	672	124	1.47 (1.06, 2.03)	1.42 (1.02, 1.99)
Q4 (165, 168)	724	163	2.03 (1.45, 2.82)	1.84 (1.32, 2.57)
Q5 (169, 188)	538	127	2.08 (1.39, 3.10)	1.90 (1.31, 2.75)
P for trend			<0.001	<0.001
Waist circumference, cm [a]				
Q1 (63.4, 85.5)	666	119	1	1

Q2 (85.6, 92.8)	659	96	0.71 (0.49, 1.03)	0.72 (0.50, 1.04)
Q3 (92.9, 99.8)	659	112	0.78 (0.55, 1.12)	0.79 (0.55, 1.14)
Q4 (99.9, 108.6)	661	139	1.04 (0.73, 1.49)	1.14 (0.79, 1.64)
Q5 (108.7, 149.3)	662	157	1.34 (0.93, 1.94)	1.37 (0.96, 1.96)
P for trend			0.02	0.01

Q: quintile.

[a] Values were cumulative averages among five visits, weighted by time interval between the visits.

[b] Events were defined as being in the highest quartile of infrarenal aortic diameters distribution (≥ 2.2 cm).

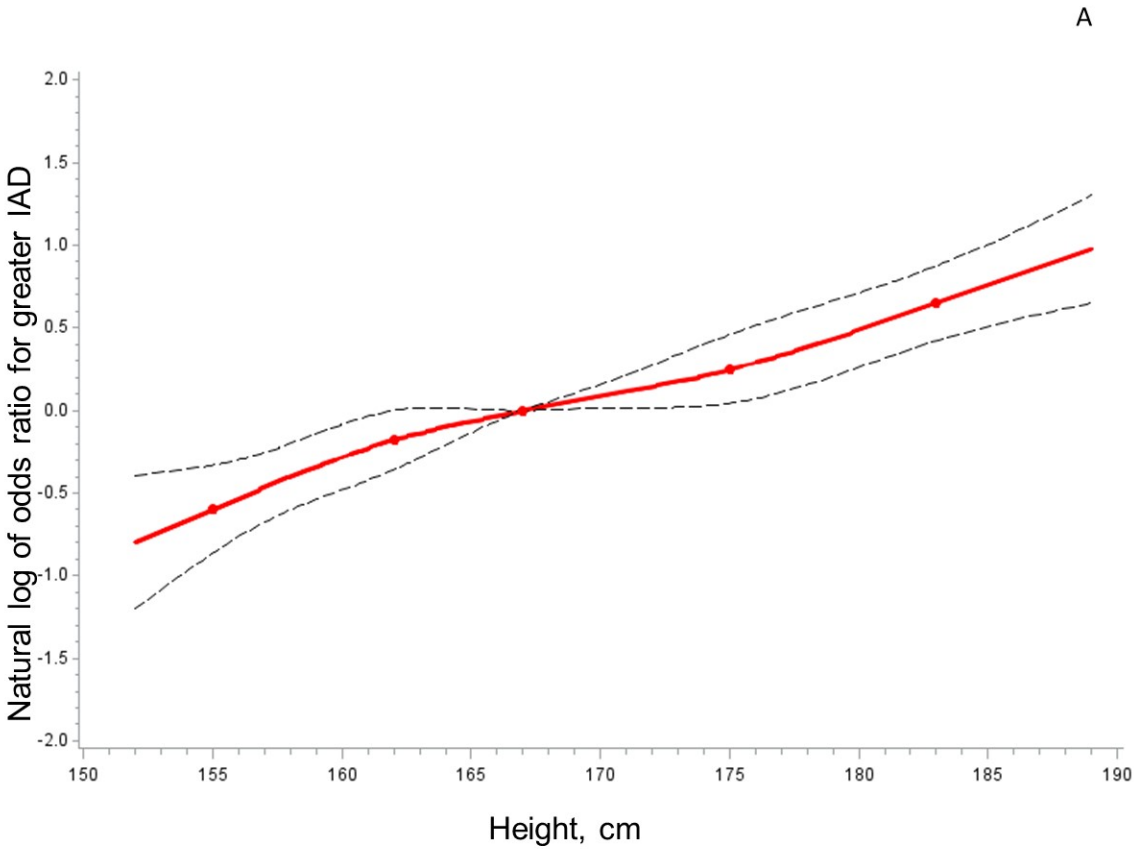
[c] Adjusted for age, race, and field center.

[d] Adjusted for age, race, field center, height, waist circumference, smoking pack years, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication use, hypertension, and diabetes.

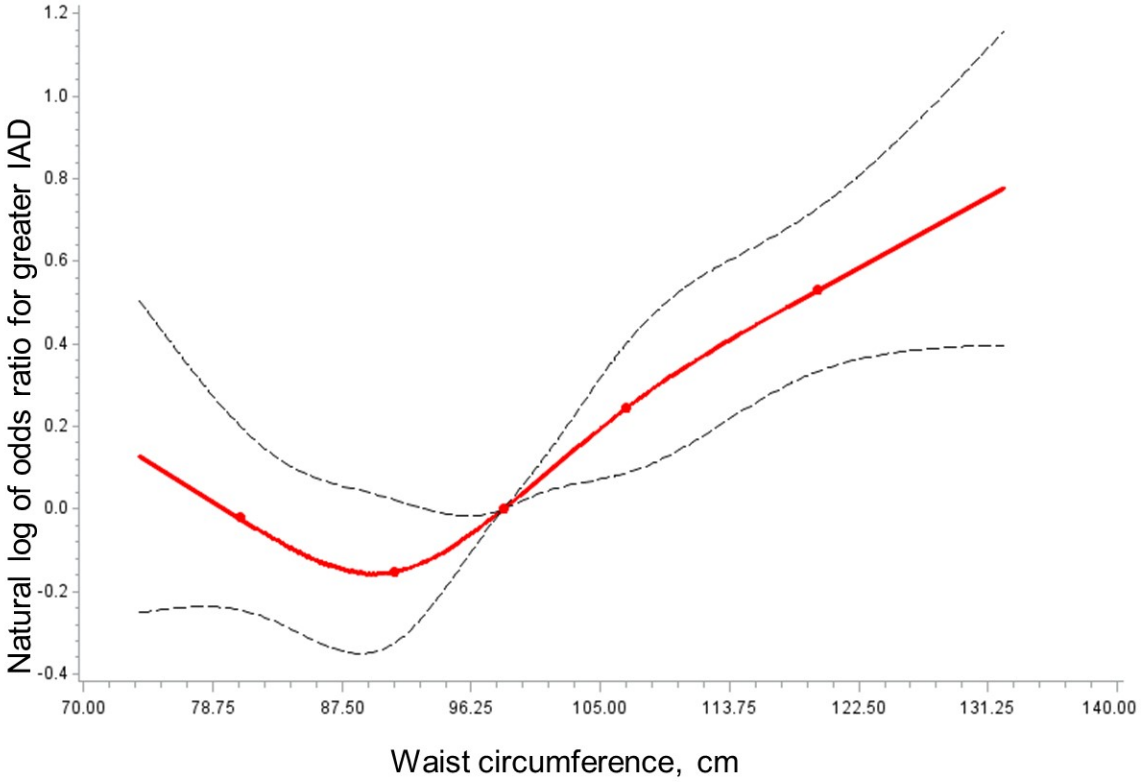
4.6 Figures

Figure 4.1 Adjusted restricted cubic splines [a] for the association between greater infrarenal aortic diameter (IAD) and (A) height, (B) waist circumference, and (C) smoking pack-year. [a] Adjusted for age, sex, race, and field center. The dotted lines indicate 95% confidence bands. Five knots were used, located at the 5th, 25th, 50th, 75th and 95th percentiles of risk factors except for smoking pack-year (45th, 55th, 70th, 85th and 95th percentiles due to a substantial proportion of non-smokers)

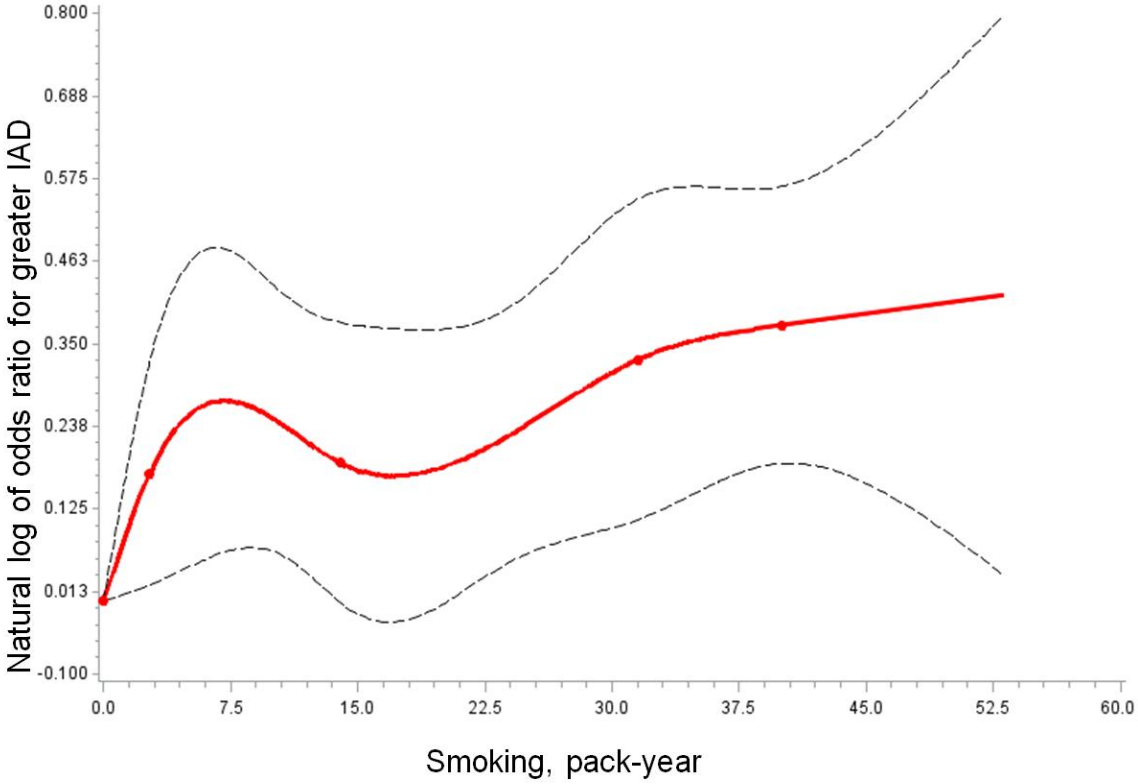
A


Natural log of odds ratio for greater IAD
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
150
155
160
165
170
175
180
185
190
Height, cm

B


Natural log of odds ratio for greater IAD
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
70.00
78.75
87.50
96.25
105.00
113.75
122.50
131.25
140.00
Waist circumference, cm

C


0.800
0.688
0.575
0.463
0.350
0.238
0.125
0.013
-0.100
Natural log of odds ratio for greater IAD
0.0
7.5
15.0
22.5
30.0
37.5
45.0
52.5
60.0
Smoking, pack-year

Chapter 5. Manuscript 3: Diabetes and Risk of Abdominal Aortic Aneurysm: A Meta-Analysis of Epidemiologic Studies

5.1 Introduction

Studies of the relationship between diabetes and abdominal aortic aneurysm (AAA) have been inconsistent. A negative association between diabetes and AAA prevalence, initially observed in a few large screening studies, was considered counterintuitive in the context of diabetes being a risk factor for various cardiovascular diseases.[37,180] Recent large case-control studies and prospective cohort studies have reported inconsistent associations between diabetes and AAA in various populations; most studies showed an inverse relationship,[48,52,57-61] while others did not show an association.[38,49,62-68]

Meta-analysis increases the power of inferences.[181] Although two meta-analyses have been conducted on the association between diabetes and AAA, they are subject to potential limitations.[56,69] For example, the one published in 2004 included only cross-sectional studies and thus may be subject to reverse causality;[56] the other study, published in 2015, pooling six cohort studies and two case-control studies was unable to examine the association by subgroups, such as population-based vs. clinical-based groups.[69] Several new studies on this topic have been published since the 2015 meta-analysis was conducted.[52,60,61,66-68] Thus, we conducted this systematic review and meta-analysis to rigorously quantify the association between diabetes (type 1 or 2) and the risk of AAA. We hypothesized that diabetes would be inversely associated with the risk of AAA.

5.2 Methods

This meta-analysis pooled results from observational studies (case-control and prospective cohort studies) available through a literature search, following standard reporting guidelines set by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[182]

5.2.1 Data searches and study selection

Investigator LY and an experienced librarian (DR) independently searched the literature and selected studies based on the same search and eligibility criteria. Disagreements were resolved by consensus in discussion with a senior investigator (WT). We used the MEDLINE online database (from 1966), EMBASE, and Web of Science until February 2018 to identify studies that examined the association between diabetes and incidence of AAA. The following key words were used: aortic aneurysm, diabetes, diabetes mellitus, hemoglobin A1c, glycated hemoglobin, glucose, case-control, prospective, and cohort. The search was limited to studies in English. In addition, we conducted a manual search of the references from selected original research and review articles.

To be eligible for inclusion in this meta-analysis, the study needed to be an original research publication with a case-control design (including incident based, nested case-control, and case-cohort) or a prospective cohort design and be conducted in adults to examine diabetes in relation to later risk of AAA. Studies were excluded if participants were < 18 years of age; neither type 1 nor

type 2 diabetes was included as the exposure variable; incident AAA risk was not reported by diabetes status; or the association estimates and measures of variance were not reported or could not be computed. When the results of a population were published more than once, only the most recent article or article including the most appropriate data (e.g., most complete adjustments for potential confounding) was included in the meta-analysis. LY reviewed all potentially relevant publications and made decisions on inclusion according to the aforementioned eligibility criteria. Another reviewer (WT) reviewed LY's literature search results and resolved disagreement by consensus.

5.2.2 Data extraction and quality assessment

Data was abstracted using a standardized data collection form. The following data were collected: article title, first and last author's names, year and source of publication, study design (case-control, cohort), setting (clinical, population), follow-up time in cohort studies, AAA ascertainment (methods, number of AAA events), diabetes definition (self-report diagnosis or treatment for diabetes, clinical records, self-report plus clinically measured diabetes, others), diabetes type (type 1, type 2, unclear), diabetes prevalence at baseline, characteristics of the study population (age, sex, race, anthropometric and lifestyle risk factors, prior disease status (including hypertension, cardiovascular disease, etc), and sample size), covariates in the fully adjustment models, relative risk of AAA, and measures of variance for association estimates. We

abstracted association estimates from the model with the most complete adjustments for potential confounders in each study.

5.2.3 Data synthesis and analysis

In the meta-analysis, we extracted data on mean (SD) or median (Interquartile range) levels of basic descriptive characteristics when appropriate for each study. An odds ratio, hazard ratio, and relative risk were treated equally in meta-analysis.[183] In the primary analysis, the pooled relative risk and its 95% confidence interval (CI) was calculated using DerSimonian and Laird random-effects models.[184] The DerSimonian and Laird random-effects model is the most widely used model in meta-analyses, as it provides conservative estimates and accounts for between-study heterogeneity.[185] The presence of heterogeneity was assessed with the Cochran's Q test and the extent of heterogeneity was quantified with the I-square index.[186] The Cochran's Q test is a statistical test to assess whether there is true heterogeneity among studies in a meta-analysis.[181] We interpreted an I-square value of < 50%, 50 - 75%, and ≥ 75% as low, moderate, and high heterogeneity, respectively.[187] If low heterogeneity between studies existed, we still used random-effects models as our primary analysis. The reason is that inherent heterogeneity did almost always exist in population characteristics, AAA ascertainment, adjustment factors, and duration of follow-up among studies included in the meta-analysis.

The potential for publication and reporting bias was assessed through the use of funnel plots, as the asymmetry of the funnel plot indicates possible

publication bias.[188] To examine the asymmetry of the funnel plot, we conducted Begg's rank correlation test and Egger's regression test.[188,189] Begg's rank test examines the correlation between association estimate and its variance, and a significant correlation (P value for correlation < 0.1) indicates significant asymmetry at the 0.1 level.[188] Egger's weighted linear regression test examines the association between the mean association estimate and its variance, and a significant association (P value for association < 0.05) rejects the hypothesis that symmetry exists in the studies included in the meta-analysis at the 0.05 level.[189]

Additionally, we conducted the following sensitivity analyses to test the robustness of the results: 1) excluding each study in turn; 2) removing studies with no clear exclusion of type-1 diabetes; 3) removing one cohort study with only 1 year of follow-up for AAA occurrence (among cohort studies only); 4) removing studies that did not use clinical records for AAA ascertainment; 5) removing studies in which association estimates were not adjusted for age, sex, race and smoking as the minimal adjustment unless the population involved primarily one sex or one race group, which was defined as a study population with ≥80% of a single sex or race group; and 6) by excluding studies with poor and fair overall quality based on the Newcastle-Ottawa Scale (≤ 5 points), a standard approach of quality scoring for observational studies.[190,191]

Finally, we conducted subgroup analyses in men and women, for a cohort design vs. case-control design, and for clinical settings vs. population settings to explore the possible relationship between diabetes and AAA in these pre-

specified subgroups. All analyses were conducted in STATA version 12 (College Station, Texas).

5.3 Results

From a total of 504 potentially relevant references, we kept 323 records after exclusion of duplicates between databases. Among the 323 records, we eliminated 291 articles after reviewing titles and abstracts, and then excluded 16 additional articles after reviewing full text articles. A total of 16 studies met all the eligibility criteria and were included in the meta-analysis (**Figure 5.1**).

Table 5.1 presents a study description and population characteristics of the 16 included studies, of which 12 were prospective cohort studies and 4 were case-control studies. Most of the prospective cohort studies (11 / 12 = 91%) were population-based, whereas most of the case-control studies (3 / 4 = 75%) were hospital or clinical-based. Follow-up time ranged from 1 to 30 years (median 10 years) across the 12 cohort studies. Diabetes was defined by clinical records in four studies, by self-reported diagnosis in ten studies, and by both self-report and clinical measurements in two studies. Measurement of AAAs also varied across studies, but most studies (12 / 16 = 75%) ascertained AAA by clinical records (hospitalization records, death certificates and/or Medicare records), three relied on imagining detecting AAA, and one study used both methods. Notably, of the 12 studies that ascertained AAAs by clinical records, five did not provide details on International Classification of Diseases (ICD) codes, five used ICD-CM codes only, and two used both ICD-CM codes and procedure codes. In addition, one

defined an AAA as an ultrasound-scanned maximum infrarenal aortic diameter (IAD) ≥ 3 cm, the second one defined an AAA as any ultrasound-scanned definite focal widening, and another defined an AAA based on both ultrasound and computed tomography scans (both used maximum IAD ≥ 3 cm as the cutpoint). Finally, one study used clinical records based on ICD-CM codes and then validated the ICD codes by ultrasound scan with a maximum IAD ≥ 3 cm. Overall, the studies included data on 2,665,121 participants with 11,410 AAAs from 12 cohort studies and 1,065 AAAs from 4 case-control studies of 12,074 participants.

Table 5.2 shows baseline characteristics of study participants in the included studies. The mean age ranged from 43.9 to 71.4 years (median 60.1 years). Seven studies were conducted in men and four were conducted in women only. All studies included predominantly white participants (overall approximately 88%) with the exception being one study where white participants constituted 40% of the population. One study was conducted in patients with clinical cardiovascular disease or people at high risk of cardiovascular disease. In that study, 81.8% participants had prevalent hypertension and 44.0% had prevalent diabetes at baseline.

Figure 5.2 presents study-specific and the pooled relative risk of AAA in relation to diabetes by the random-effects model. Comparing those with diabetes to those without, the pooled relative risk (95% CI) for AAA from the 16 studies was 0.56 (0.50, 0.63). Heterogeneity in the relative risk estimates among studies

was low as I^2 (18.7%), and the test of heterogeneity was not statistically significant (P = 0.24).

There was no evidence of publication bias using either Begg's rank correlation (P = 0.37) or Egger's linear regression tests (P = 0.28). The funnel plot with pseudo 95% CI is presented in **Figure 5.3.**

In sensitivity analyses, the exclusion of any one study from the analysis did not significantly alter the pooled relative risk (**Figure 5.4**). Also, the inverse association between diabetes and AAA became slightly stronger when only studies of type-2 diabetes were included [studies remaining in the meta-analysis: N = 2; 0.45 (0.36, 0.56)] (**Figures 5.5 - 5.6**). Results were similar by excluding studies in which AAAs were not ascertained using clinical records [N = 10; 0.56 (0.50, 0.64)], by removing one cohort study with 1-year follow-up [N = 11; 0.57 (0.48, 0.68)], or by removing studies which reported unadjusted estimates or estimates without adjustment for age, sex, race, and smoking [N = 9; 0.55 (0.47, 0.64)] (**Figures 5.7 - 5.9**). Overall study quality scores are presented in **Tables 5.3 and 5.4** for cohort studies and case-control studies, respectively. The inverse association between diabetes and AAA remained consistent [N = 12; 0.54 (0.47, 0.61)] after removing studies with low or moderate overall study quality (Newcastle-Ottawa score ≤ 5) (**Figure 5.10**).

Results of subgroup analyses by sex, study design, and setting are presented in **Table 5.5**. As in the primary analysis, an inverse association between diabetes and incident AAA was observed within each subgroup. The

pooled relative risk (95% CI) was 0.58 (0.51, 0.66) in cohort studies, 0.42 (0.29, 0.60) in case-control studies, 0.53 (0.42, 0.66) in studies conducted in clinical settings, and 0.57 (0.48, 0.68) in studies conducted in population settings. Similar associations were seen in men [0.58 (0.46, 0.74)] and women [0.67 (0.32, 1.43)], although the pooled relative risk in women was not statistically significant (N of studies = 4) (**Figures 5.11 - 5.14**).

5.4 Discussion

This meta-analysis of case-control and prospective cohort studies suggested that diabetes is inversely related to the risk of incident AAA in both general and patient populations. We observed low between-study heterogeneity and no evidence of publication bias.

Our findings contradict the 2004 meta-analysis of cross-sectional studies which did not find a significant association between diabetes and prevalent AAA.[56] Since the 2004 meta-analysis only included cross-sectional studies, it was subject to potential limitations such as survival bias. A 2015 meta-analysis pooled data from case-control studies (114 AAAs and 195 non-AAAs) and prospective cohort studies (6,403 AAAs and 643,896 non-AAAs). That meta-analysis reported a negative association between diabetes and AAA.[69] However, the 2015 meta-analysis included only two case-control studies and six cohort studies, with three of the cohort studies not adjusting for potential confounding variables, including age, sex, race, and smoking. Moreover, the 2015 meta-analysis had insufficient data to explore whether the diabetes-AAA relation

differed by other factors such as study design and setting. In contrast, our meta-analysis included 4-times as many subjects than the 2015 meta-analysis was able to examine associations by subgroups. Our meta-analysis was also able to examine the association among studies that did minimal adjustment (eg, adjusting for age, sex, race, and smoking). Our study confirmed an inverse association between diabetes and AAA, which remained in subgroups of cohort vs. case-control studies, a population setting vs. clinical setting, and males vs. females.

There are several possible mechanisms that might mediate the negative association between diabetes and AAA. First, hyperglycemia reduces proteolysis of matrix in the arterial wall. Hyperglycemia reduces concentrations of MMP-2 and MMP-9, both of which degrade extracellular matrix and promote the development of AAAs through their proteolytic effects.[175] Hyperglycemia is associated with lower aortic wall stress,[103,104] which prevents AAA development.[192] Hyperglycemia might also decelerate arterial matrix loss by increasing collagen synthesis.[173,176,177] The advanced glycation products associated with diabetes have been shown to resist proteolysis, inhibit secretion of MMPs, and increase matrix proteins by increasing smooth muscle cell proliferation and inducing cross-linking of collagen lattices in the aortic media.[178,179] Diabetes may also suppress elevated plasmin[193] and increased cell division autoantigen 1, both of which are key factors of extracellular matrix degradation and initiation of fibrinolysis.[194,195] All of the above mechanisms due

to hyperglycemia are consistent with population-based studies in which continuous levels of fasting glucose and hemoglobin A1c are inversely associated with AAA risk.[196,197] It is unclear whether insulin resistance is related to AAA. In a cohort study, fasting insulin was not associated with AAA risk.[45]

Our findings contradict the results from a Mendelian Randomization study conducted in Dutch descent.[70] That Mendelian Randomization study did not show an association between AAA and the instrumental variable defined by the genotypes of 65 single-nucleotide polymorphisms associated with type-2 diabetes, suggesting that type-2 diabetes was not associated with AAA.[70] However, Mendelian randomization study results should be interpreted with caution because of possible limitations related to the assumptions of Mendelian randomization analysis, such as potential pleiotropic effects, weak instruments, etc.[75] Nevertheless, the following two aspects should also be concerned when interpreting our results. First, it is possible that the inverse relation between diabetes and AAA observed in our study is confounded. For example, the negative association of diabetes with AAA may be attributable to the use of some diabetic medications. Metformin has been suggested to improve aortic wall elasticity, and decrease mural macrophages, smooth muscle cell proliferation and neovessel density in the aortic wall.[170,171] Rosiglitazone and pioglitazone may decrease expression of matrix metalloproteinases in the aortic wall.[173,174] Anti-inflammatory effects of thiazolidinediones have been reported in animal models.[172] Nonetheless, existing observational studies are unable to disentangle

the effects of medication use on the diabetes-AAA relation. Therefore, more evidence is needed to establish or refute a causal, inverse relationship between diabetes and AAA.

The present study has some limitations. First, information on some potential confounders was missing in the included studies. Since individual data were not available, we had to use association estimates after adjustment for local confounders at the study level and then pool them across studies. However, results were similar after removing studies that reported unadjusted or insufficiently adjusted association estimates. Nonetheless, residual confounding cannot be eliminated, as in other observational studies. An individual-level meta-analysis using complete data would be more desirable. Second, we were not able to examine the type of diabetes in relation to AAA risk due to lack of detailed information in many of the included studies. Although only two studies had a clear statement that they included type-2 diabetes only, type-2 diabetes was likely analyzed in most studies because the vast majority of diabetes cases in adult population are type-2.[198] Nonetheless, a sensitivity analysis among the two studies including type-2 diabetes explicitly showed consistent results. On the other hand, there are several strengths in the present study. We conducted this meta-analysis following a stringent protocol.[182] This meta-analysis has a large sample size and a number of high-quality studies,[191] which provided sufficient power to detect statistically significant association estimates, assess publication bias, and conduct subgroup analysis.

In conclusion, this meta-analysis of case-control and prospective cohort studies suggests that diabetes is strongly and inversely associated with the risk of AAA. The findings are contrary to the fact that diabetes is a risk factor for most other cardiovascular diseases. Since the underlying pathophysiological pathways are intricate and uncertain, future studies are warranted to further investigate the potential mechanisms mediating the negative association between diabetes and AAA.

5.5 Tables

Table 5.1 Characteristics of included studies

Author	Year	Setting	Design	Follow-up year	N total	N case	DM definition	AAA ascertainment	AAA definition	Covariates
Baumgartner	2008	clinical	cohort	1	68236	1752	DM treatment record	clinical records	Not provided	age, sex, race, smoking, HTN, and dyslipidemia
Blanchard	2000	clinical	case-control	N/A	200	98	FG ≥7 mmol/L or self-reported DM diagnosis or DM treatment	ultrasound scan	Any definite focal widening classified as AAA, 92% ≥3 cm	age, sex, smoking, and family history
Franks	1996	clinical	case-control	N/A	288	44	self-reported DM diagnosis	clinical records	Not provided	age and sex matched
Iribarren	2007	population	cohort	13	104813	605	self-reported DM diagnosis	clinical records	ICD-9:441.3, 441.4	age, sex, race, education, height, weight, smoking, alcohol, white blood cell

										counts, chronic kidney disease, HTN, CVD, and hormone use.
Jahangir	2015	population	cohort	4.9	18782	281	self-reported DM diagnosis	clinical records	ICD-9:441.3, 441.4	sex, race, education, BMI, smoking, CVD, and HTN
Lederle	2008	population	cohort	7.8	161808	184	self-reported DM diagnosis	clinical records	Not provided	age, sex, race, height, weight, smoking, alcohol, CVD, HTN, COPD, hormone use, and lipid meds
Ohrlander	2012	population	cohort	13	246957	3335	DM treatment record	clinical records	ICD-10: I71.3, I71.4	age, income, HTN, CVD and COPD
Robin	2003	population	cohort	30	19274	418	self-reported DM diagnosis	clinical records	ICD-9: 441.3, 441.4 ICD-10: 71.3, 71.	N/A
Shah	2015	population	cohort	5.5	1921260	3051	DM treatment record	clinical records	Not provided	age, sex, deprivation, BMI, smoking, lipids and

										lipid meds, BP and BP meds
Smelser	2014	clinical	case-control	N/A	11411	888	type-2 diabetes related death and hospital discharge records	Clinical records and ultrasound scan	ICD-9: 441.3, 441.4 Max IAD ≥3 cm	age and sex matched
Tang	2016	population	Cohort	22.5	15703	588	FG ≥7 mmol/L or Non-FG ≥11.1 mmol/L, self-reported DM diagnosis and treatment	clinical records	ICD-9: 441.3, 441.4 ICD-10: 71.3, 71.4 Procedure code 38.44, 39.71	age, sex, race, height, smoking, alcohol, lipids, HTN and PAD
Tornwall	2001	population	cohort	5.8	29133	181	self-reported DM diagnosis	clinical records	ICD-8:441.00-441.99 ICD-9: 441.0A-441.9x Procedure code: 39.71	age, education, BMI, smoking, physical activity, BP, lipids, and trial group
Wanhainen	2005	population	case-	N/A	175	35	self-reported DM	ultrasound and	Mean max IAD by	N/A

			control				diagnosis	computed tomography scan	the two methods ≥3 cm	
Wong	2007	population	cohort	4	39352	376	self-reported DM diagnosis	clinical records	Not provided	age, smoking, BMI, physical activity, HTN and dyslipidemia,
Stackelberg	2017	population	cohort	13	14249	168	self-reported DM diagnosis	ultrasound scan or self-reported treatment	Max IAD ≥3 cm	education, smoking, BMI, WC, diet, physical activity, alcohol intake, HTN, CVD, and dyslipidemias
Wang	2017	population	cohort	10.4	25554	471	self-reported DM diagnosis	Self-reported diagnoses, clinical records	ICD-9: 441.3, 441.4	age, race, trial assignment, BMI, smoking status, alcohol use, physical activity, and history of HTN, CVD dyslipidemias

AAA, abdominal aortic aneurysm; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes; FG, fasting glucose; IAD, infrarenal aortic diameter; HTN, hypertension; NDI, National Death Index; PAD, peripheral artery disease

Table 5.2 Baseline characteristics of study populations

Author	Mean age (SD), year	Male	White	Mean height, cm	Current smoking	HTN	Diabetes	Comorbidities
Baumgartner	68.6 (10.1)	63.0%	67.2%	N/A	14.8%	81.8%	44.0%	With established CVD, or with ≥3 atherothrombotic risk factors
Blanchard	69.0	51.0%	100.0%	N/A	26.9%	38.4%	14.5%	Not indicated
Franks	70.4 (10.5)	83.0%	100.0%	172	100.0%	20.7%	6.3%	Not indicated
Iribarren	43.9 (14.1)	44.8%	82.0%	167	37.3%	36.5%	3.2%	Not indicated
Jahangir	64.4 (5.6)	63.9%	40.0%	168	21.2%	71.3%	30.0%	Not indicated
Lederle	63.2 (7.2)	0.0%	82.5%	162	6.9%	38.9%	5.9%	Not indicated
Ohrlander	71.4	43.4%	100%	N/A	N/A	N/A	2.4%	Not indicated
Robin	50.5 (6.6)	54.9%	94.9%	169	38.0%	59.1%	3.4%	Not indicated

Shah	46.9 (14)	49.4%	90.0%	N/A	20.5%	N/A	1.8% [b]	Not indicated
Smelser	N/A	42.2%	100.0%	N/A	N/A	N/A	N/A [b]	Not indicated
Tang	54.2 (5.8)	44.8%	72.9%	169	26.1%	35.0%	11.9%	Not indicated
Tornwall	57 (53-61) [a]	100.0%	100.0%	N/A	100.0%	N/A	4.0% [a]	Not indicated
Wanhainen	N/A	83.0%	100.0%	N/A	12.0%	43.2%	11.4%	Not indicated
Wong	53.3	100.0%	N/A	N/A	9.6%	19.3%	2.0%	Not indicated
Stackelberg	55.3 (4.2)	100%	100%	N/A	22.3%	17.9%	4.6%	Not indicated
Wang	65.5 (8.3)	100%	90.50%	N/A	3.8%	45.9%	7.6%	Not indicated

CVD, cardiovascular disease; HTN, hypertension

[a] Median value (Interquartile range).

[b] Type-2 diabetes only.

Table 5.3 Newcastle-Ottawa Scale assessments for cohort studies (a study can be awarded a point for each of the nine items)

Study	Selection [a]				Comparability [b]		Outcome [c]			Score
	External validity	Selection of the non-exposed cohort	Ascertainment of exposure to implants	No outcome present at baseline	Controls for the most important factor	Controls for any additional factor	Outcome assessment	Follow up long enough	Adequacy of follow up	
Tornwall (2001)	0	1	0	0	1	1	1	1	1	6
Robin (2003)	0	1	0	0	0	1	1	1	1	5
Iribarren (2007)	1	1	0	0	1	1	1	1	1	7
Wong (2007)	1	1	0	0	0	1	1	1	1	6
Baumgartner (2008)	0	1	1	1	1	1	1	0	1	7
Lederle (2008)	1	1	0	0	1	1	1	1	1	7
Ohrlander (2012)	0	1	1	1	0	1	1	1	1	7
Jahangir (2015)	0	1	0	0	0	1	1	1	1	5

Shah (2015)	1	1	1	0	1	1	1	1	1	8
Tang (2016)	1	1	1	0	1	1	1	1	0	7
Stackelberg (2017)	0	1	0	0	0	1	1	1	1	5
Wang (2017)	1	1	0	0	1	1	1	1	1	7

[a] Within the Selection category. External validity: the exposed cohort is truly or somewhat representative of the average demographics in the community (1 point); Selection of the non-exposed cohort: drawn from the same community as the exposed cohort (1 point); Ascertainment of exposure to implants: secure record (eg surgical records) or structured interview (1 point); No outcome present at baseline: demonstration that outcome of interest was not present at start of study: yes (1 point);

[b] Within the Comparability category. Comparability of cohorts on the basis of the design or analysis: study controls for the most important factor (1 point); study controls for any additional factor (1 point; this criteria could be modified to indicate specific control for a second important factor);

[c] Within the Outcome category. Outcome assessment: independent blind assessment or record linkage (1 point); Follow up long enough: was follow-up long enough for outcomes to occur: yes (1 point; select an adequate follow up period for

outcome of interest); Adequacy of follow up: complete follow up, or small number lost to follow up, or description provided of those lost (1 point)

Table 5.4 Newcastle-Ottawa Scale assessments for case-control studies (a study can be awarded a point for each of the nine items)

Study	Selection [a]				Comparability [b]		Exposure [c]			Score
	Adequate case definition	Case representati-veness	Control selection	Control definition	Controls for the most important factor	Controls for any additional factor	Exposure ascertainment	Same method of ascertainment for cases and controls	Non-response rate	
Franks (1996)	1	0	1	0	1	0	0	1	0	4
Blanchard (2000)	0	1	1	1	1	0	1	1	1	7
Wanhainen (2005)	0	1	1	1	0	0	0	1	1	6
Smelser (2014)	1	1	1	1	0	0	1	1	1	7

[a] Within the Selection category. Adequate case definition: is the case definition adequate: Yes with independent validation (1 point); Case representativeness: consecutive or obviously representative series of cases (1 point); Control selection: community controls (1 point); Control definition: no history of endpoint (1 point);

[b] Within the Comparability category. Comparability of cases and controls on the basis of the design or analysis: study controls for the most important factor (1 point); Study controls for any additional factor (1 point; this criteria could be modified to indicate specific control for a second important factor);

[c] Within the Exposure category. Exposure ascertainment: secure record (e.g. surgical records) or structured interview where blind to case/control status (1 point); Same method of ascertainment for cases and controls: yes (1 point); Non-Response rate: same rate for both groups (1 point)

Table 5.5 Subgroup analyses by sex, design, and setting

	No. study	Fixed-effects model	Random-effects model
Overall	16	0.57 (0.53, 0.62)	0.56 (0.50, 0.63)
By sex			
Men	7	0.60 (0.49, 0.73)	0.58 (0.46, 0.74)
Women	4	0.68 (0.48, 0.97)	0.67 (0.32, 1.43)
By design			
Cohort	12	0.58 (0.53, 0.64)	0.58 (0.51, 0.66)
Case control	4	0.42 (0.29, 0.60)	0.42 (0.29, 0.60)
By setting			
Clinical setting	4	0.57 (0.51, 0.64)	0.53 (0.42, 0.66)
Population setting	12	0.57 (0.50, 0.66)	0.57 (0.48, 0.68)

Figure 5.1. Flow diagram of systematic review (as of Feb 2018)

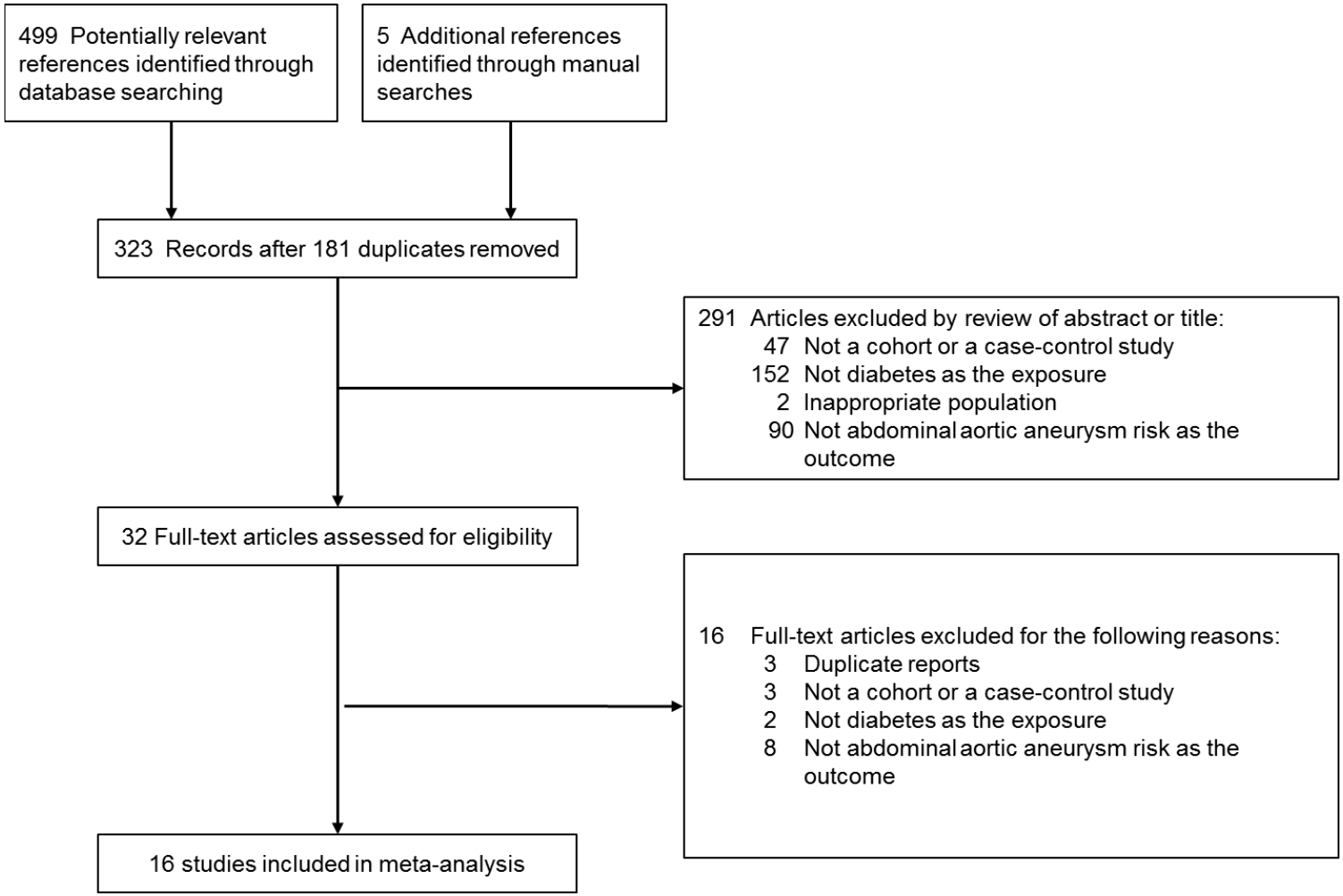


Figure 5.2. Pooled relative risk (95% confidence interval, CI) of abdominal aortic aneurysm in relation to diabetes (yes, no) (n = 16 studies)

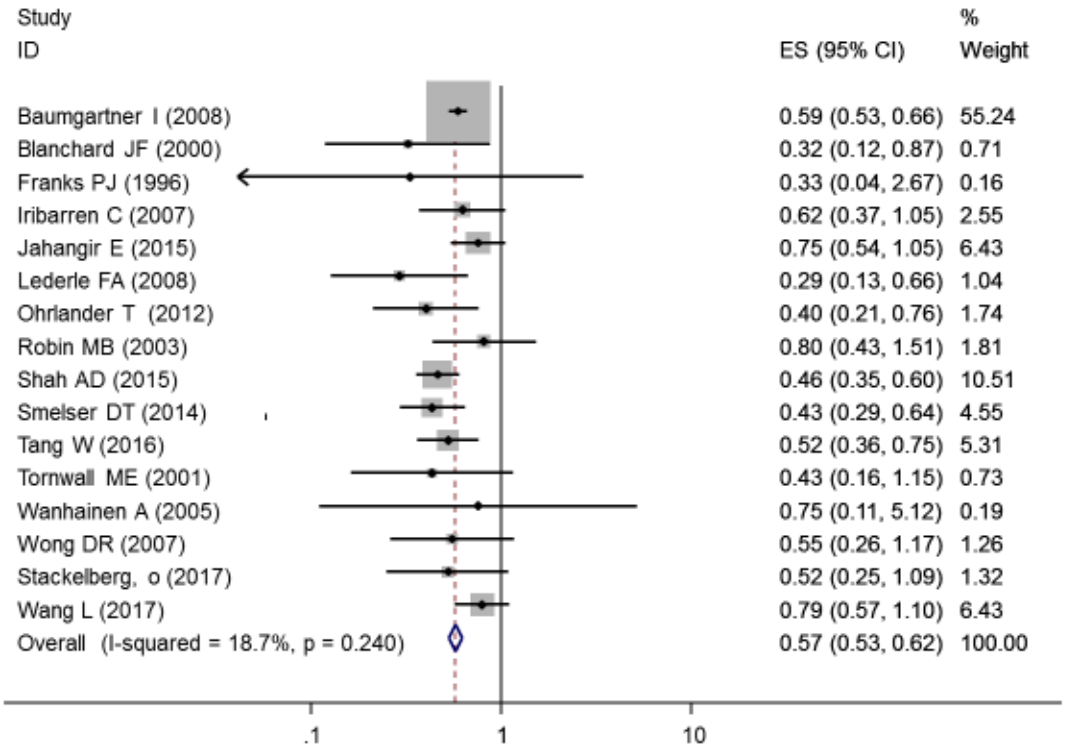


Figure 5.3 Funnel plot with pseudo 95% confidence limits to test potential publication bias. RR: relative risk.

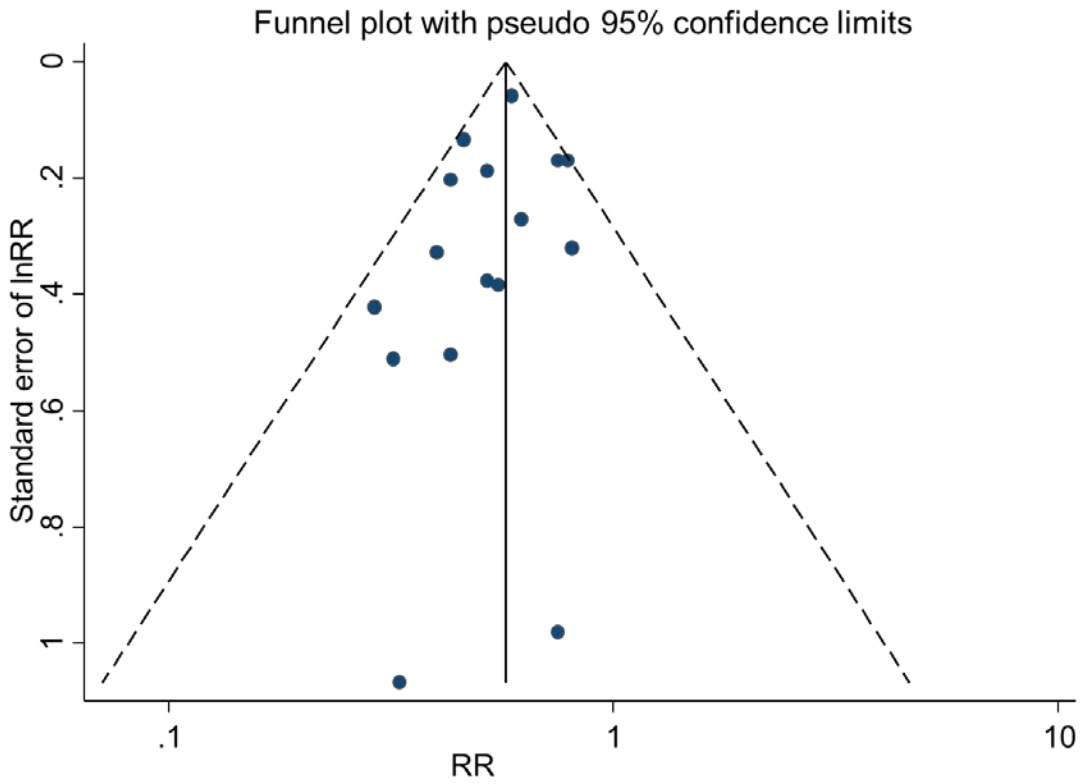


Figure 5.4 Sensitivity analysis using random-effects model by excluding each study in turn.

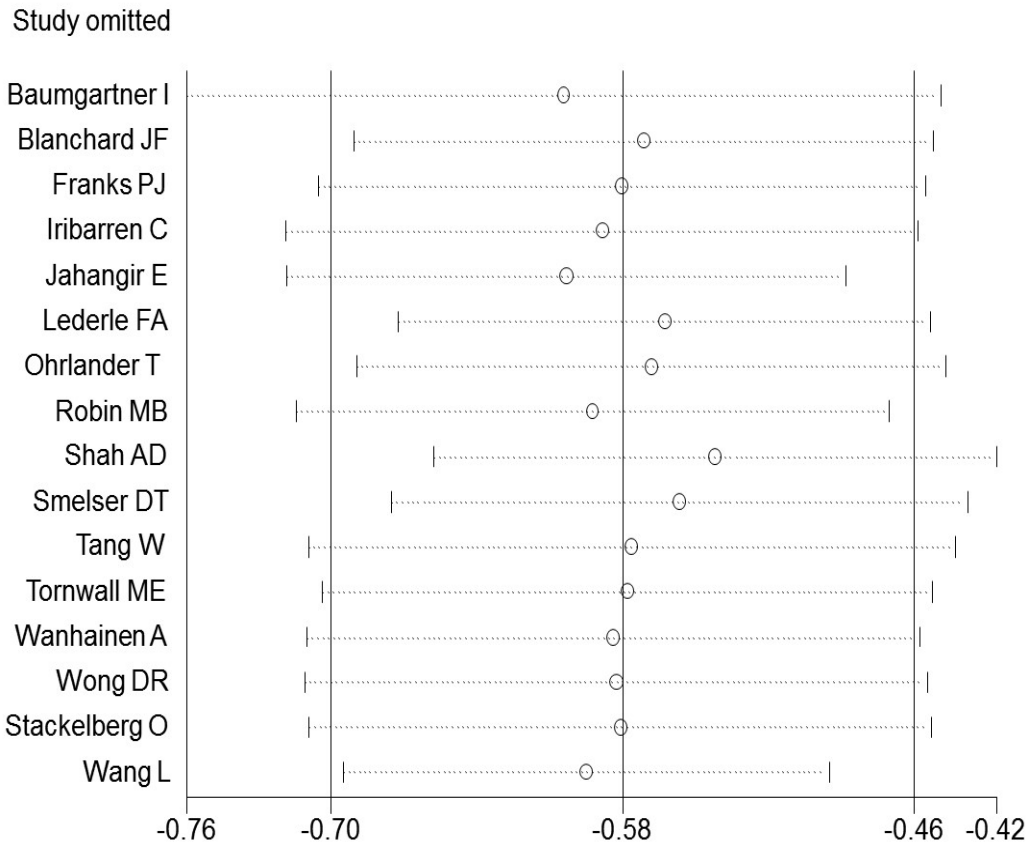


Figure 5.5 Relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a random-effects model by removing studies in cardiovascular disease patients (n studies = 15)

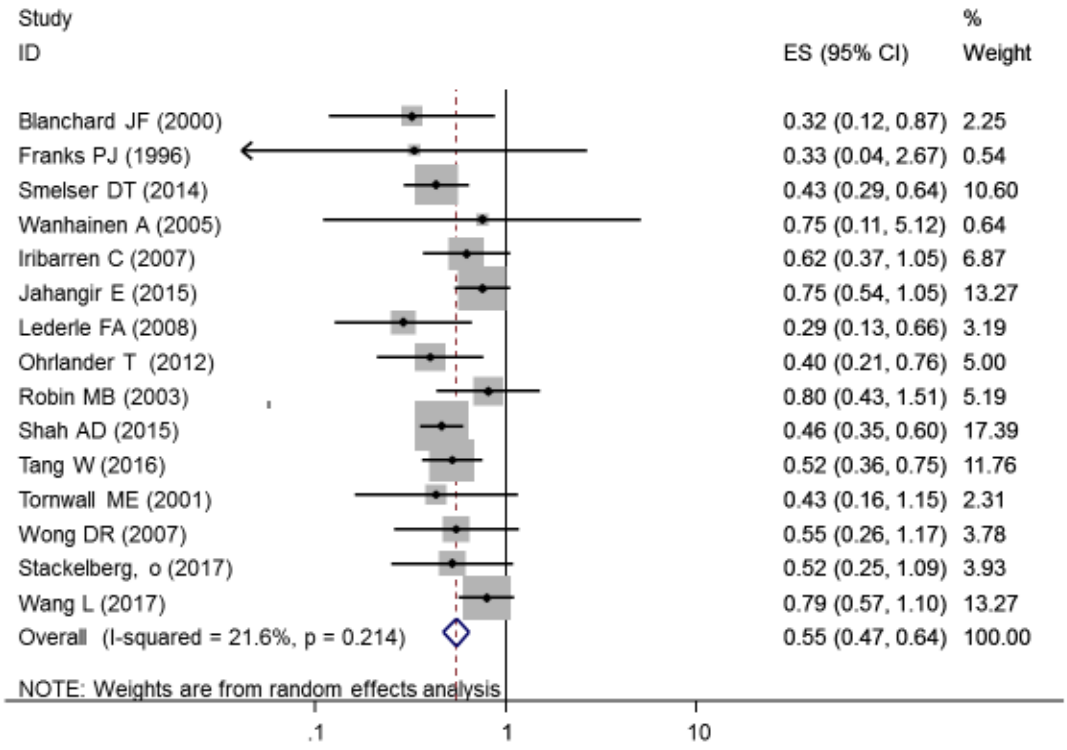


Figure 5.6 Relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a random-effects model by removing studies with no clear exclusion of type 1 diabetes (n studies = 2)

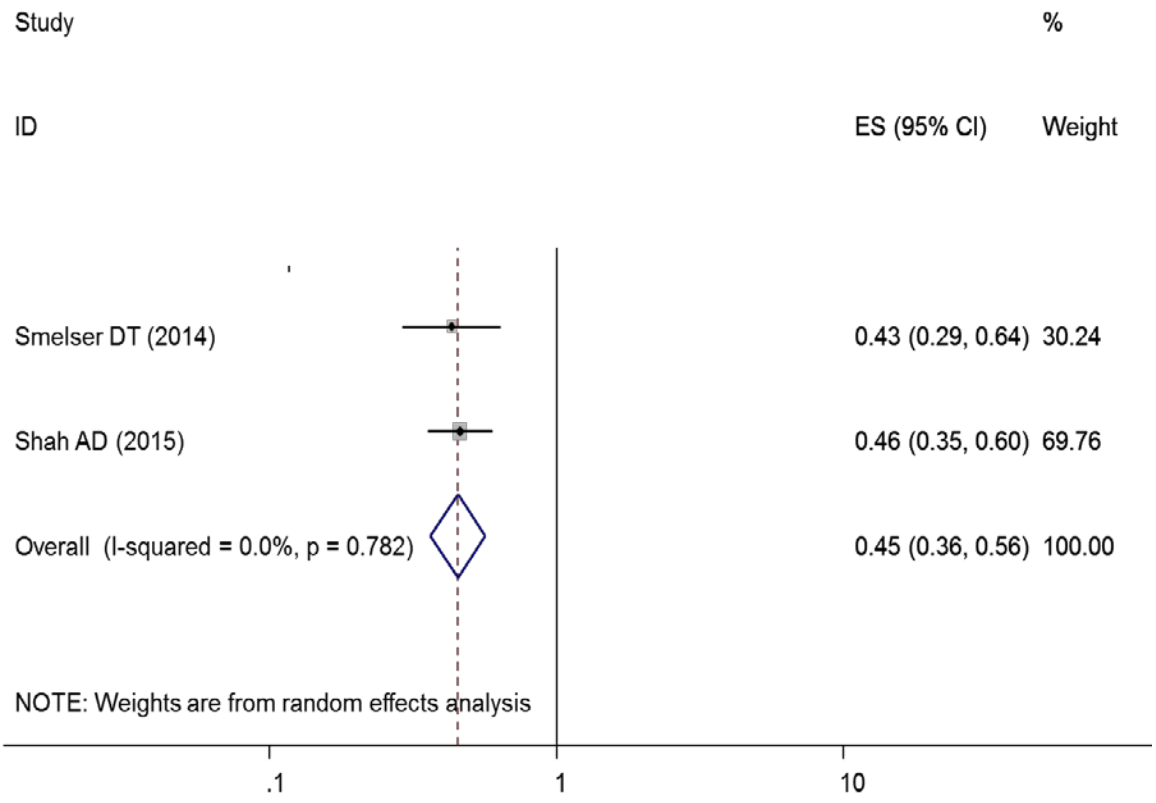


Figure 5.7 Relative risk (95% confidence interval) of abdominal aortic aneurysm (AAA) in relation to diabetes (yes, no) using a random-effects model by removing studies where AAA was not ascertained using clinical records (n studies = 14)

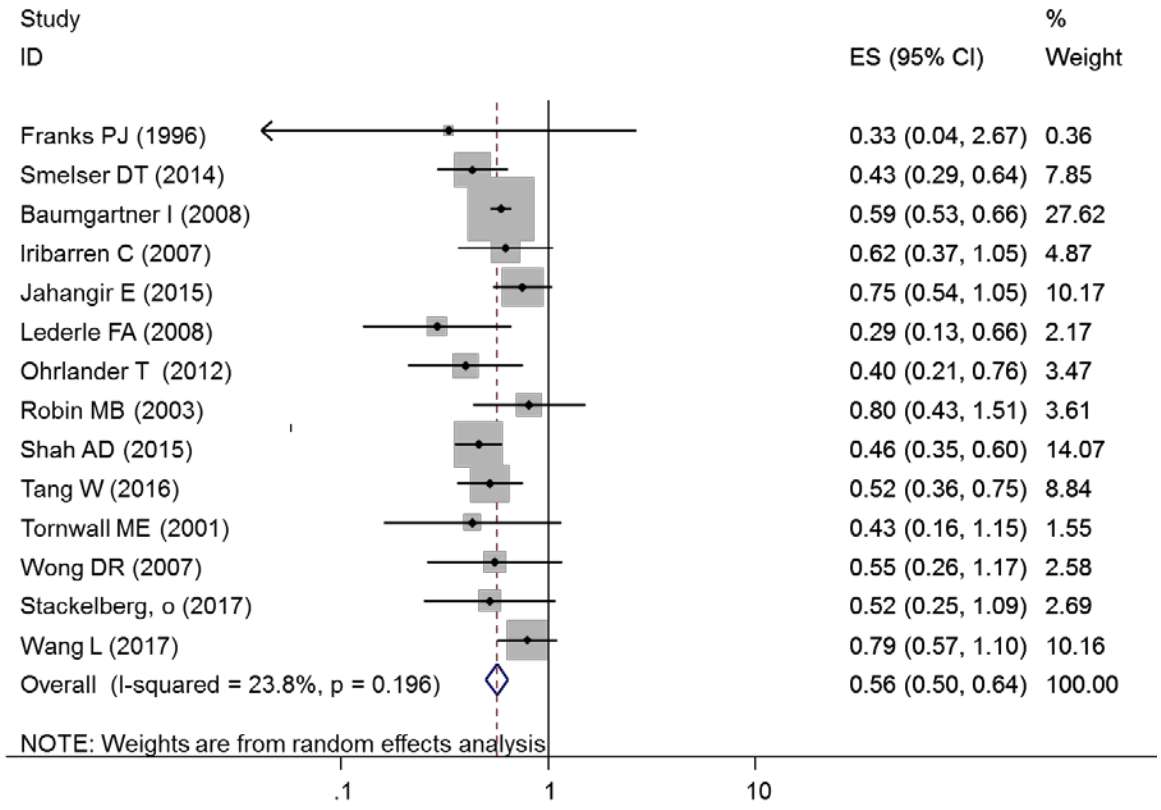


Figure 5.8 Relative risk (95% confidence interval) of abdominal aortic aneurysm (AAA) in relation to diabetes (yes, no) using a random-effects model by removing studies with insufficient follow up time (n studies = 11)

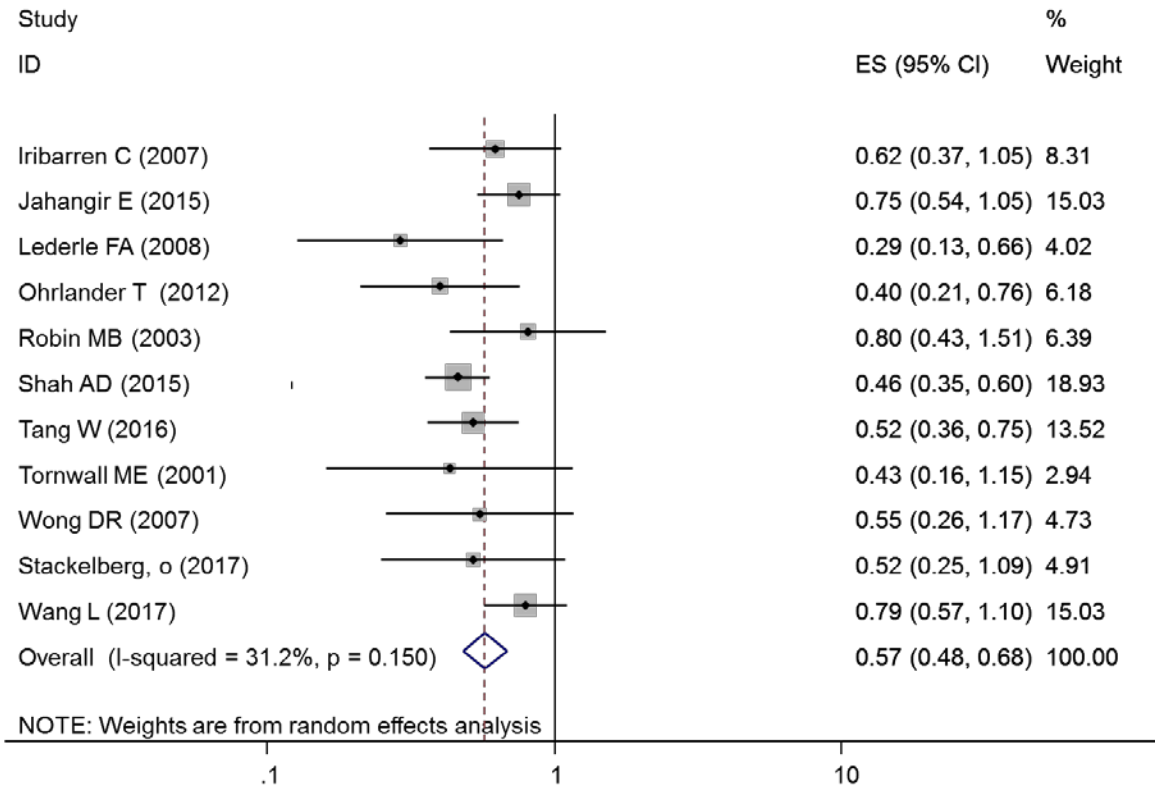


Figure 5.9 Relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a random-effects model by removing studies with inadequate adjustment (age, sex, race, and smoking; n studies = 9)

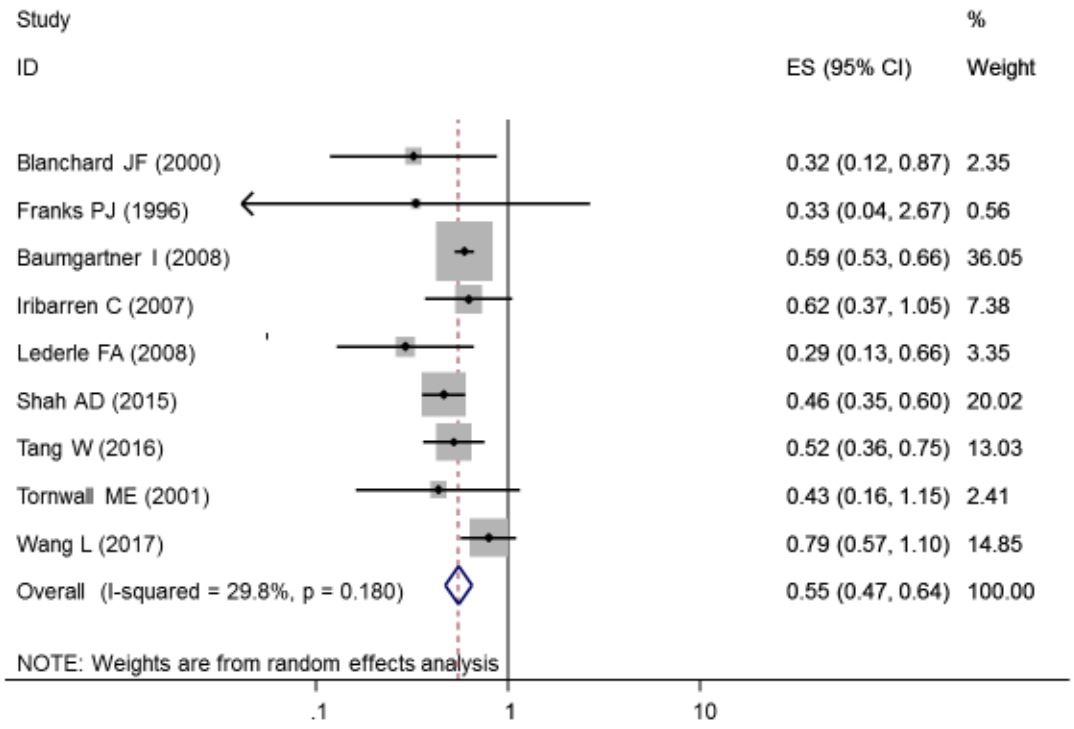


Figure 5.10 Relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a random-effects model by removing studies with low and moderate overall study quality (Newcastle-Ottawa score ≤5) (n studies = 12)

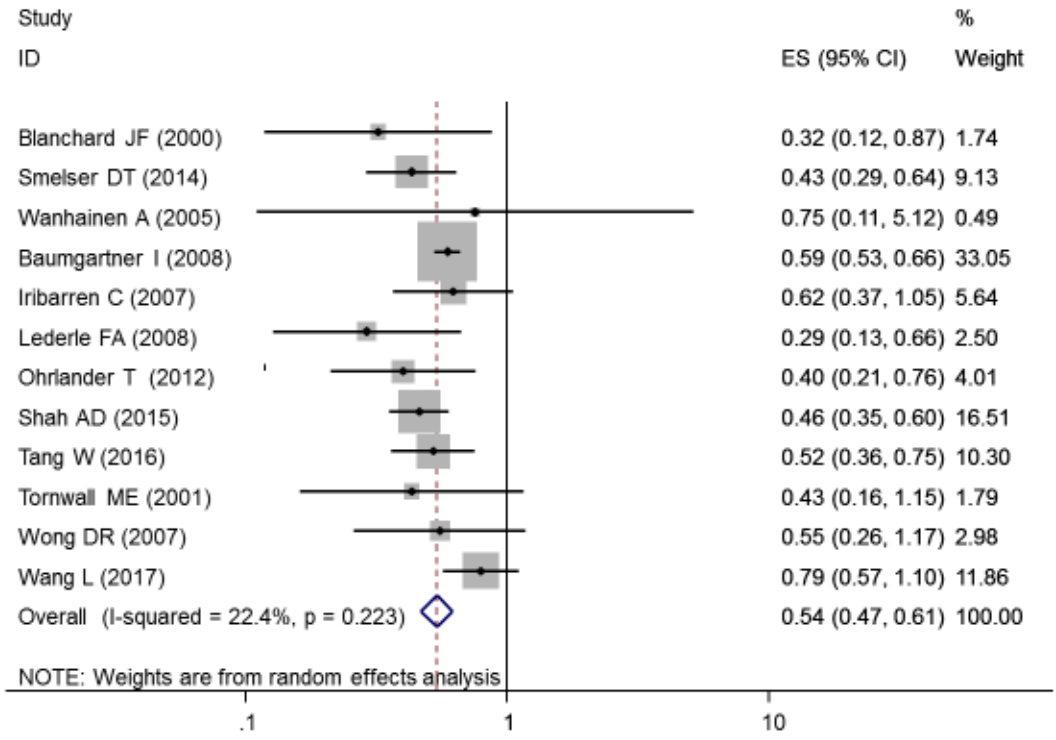


Figure 5.11 Pooled relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) (n = 16 studies) using a random-effects model by study design (cohort/case-control)

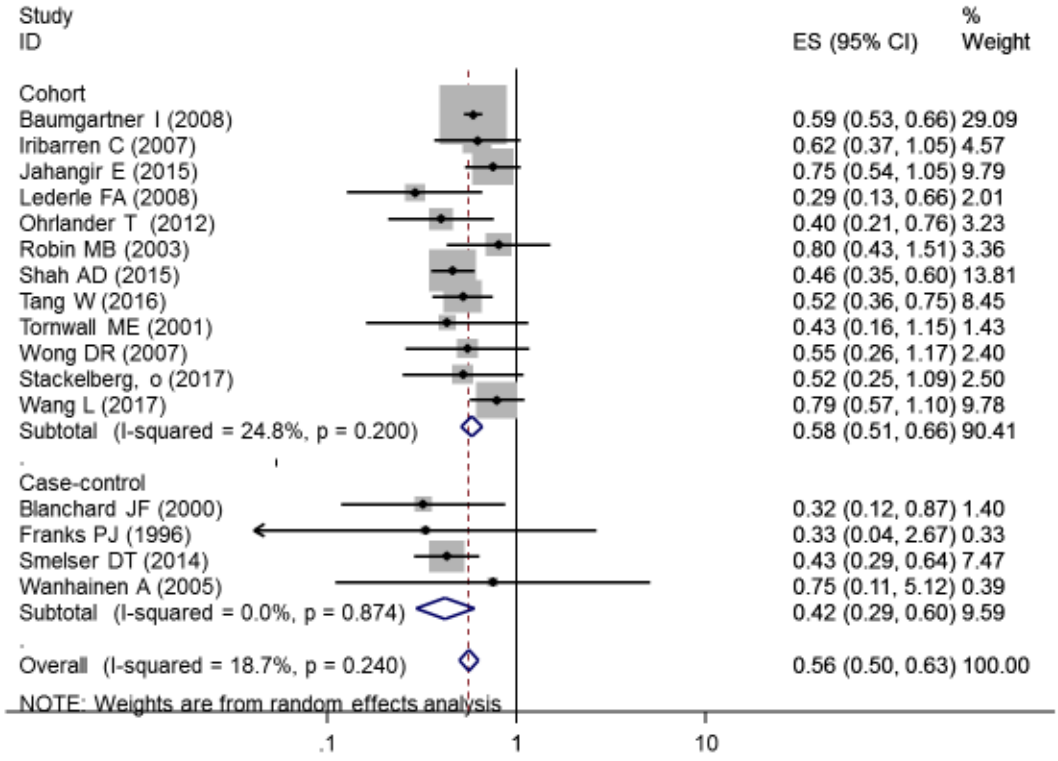


Figure 5.12 Pooled relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) (n = 16 studies) using a random-effects model by setting (clinical/population)

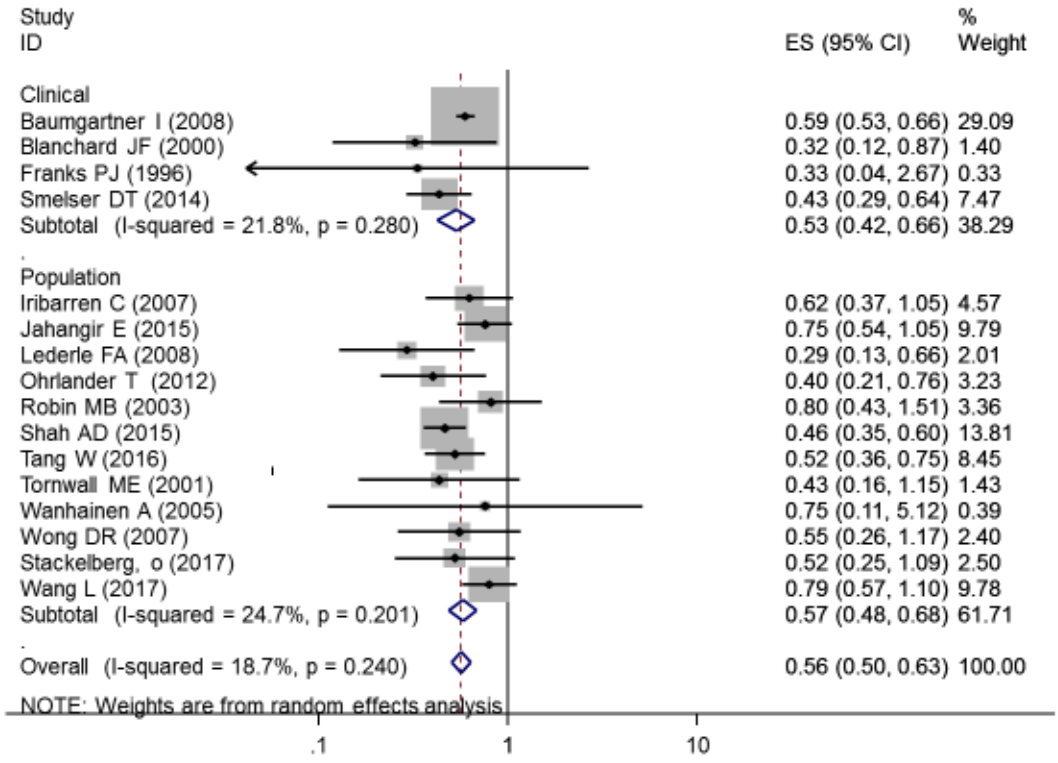


Figure 5.13 Pooled relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a random-effects model among men (n = 7 studies)

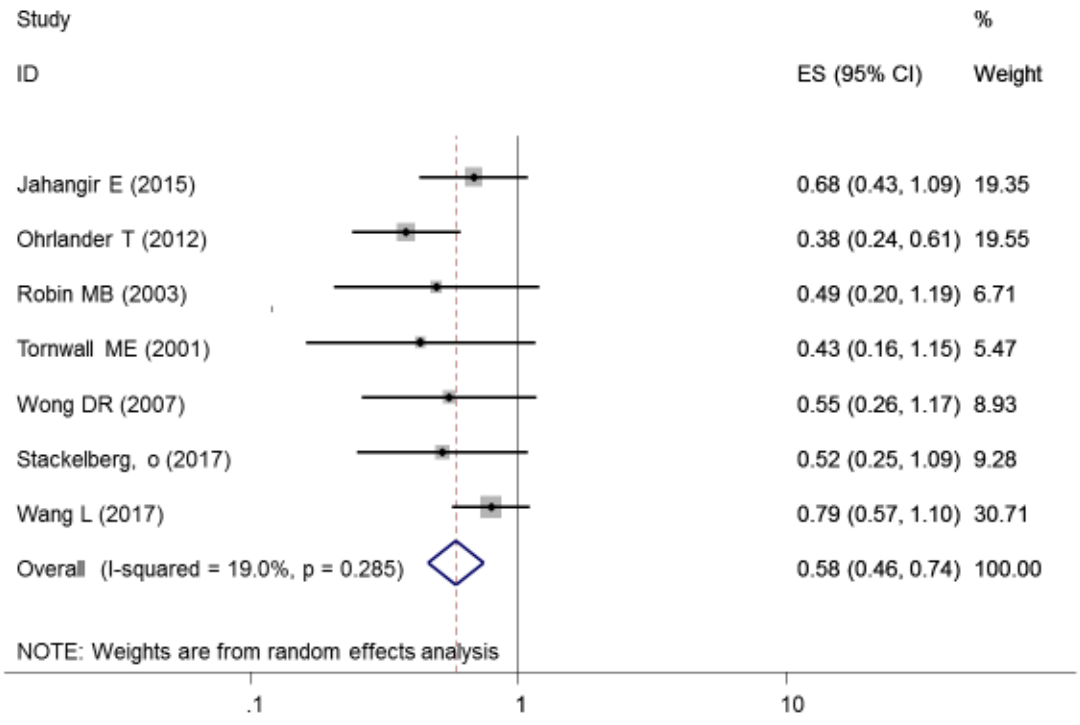


Figure 5.14 Pooled relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a random-effects model among women (n = 4 studies)

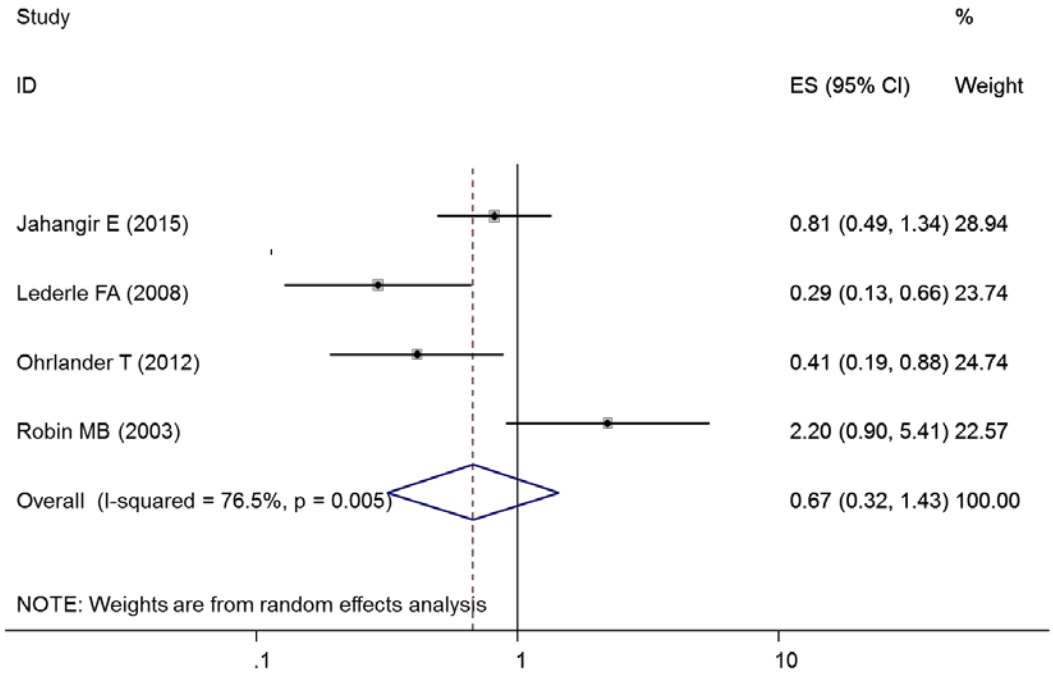


Figure 5.15 Pooled relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) (n = 16 studies) using a fixed-effects model

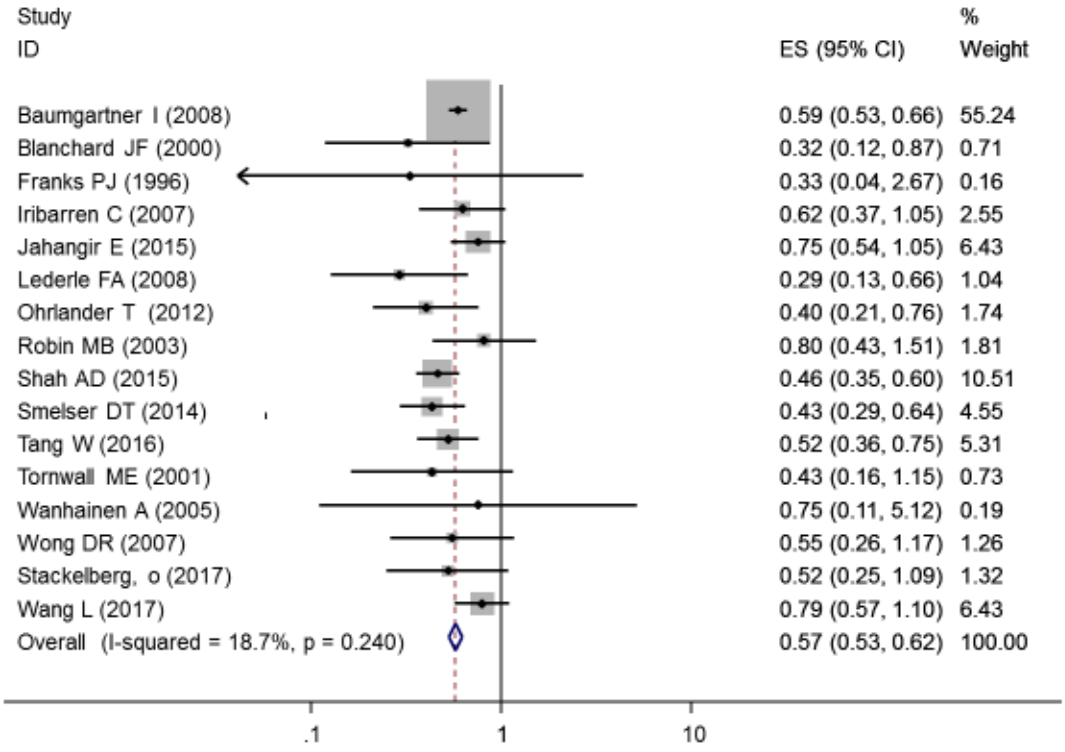


Figure 5.16 Relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a fixed-effects model by removing each study in turn

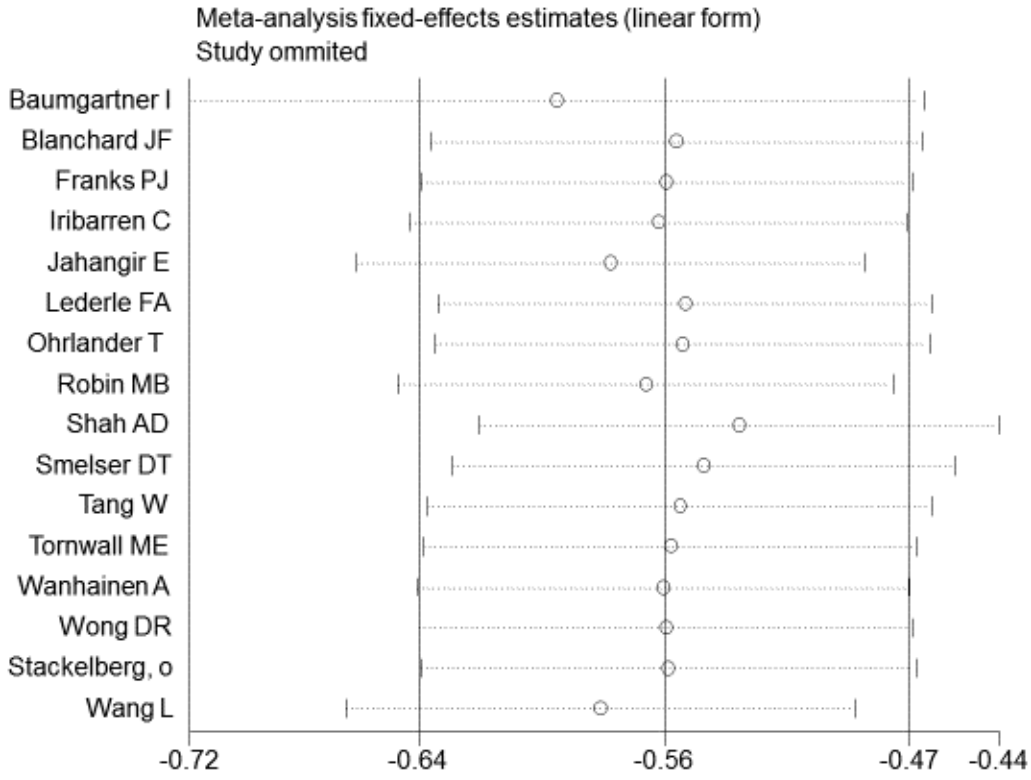


Figure 5.17 Relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a fixed-effects model by removing studies in cardiovascular disease patients (n studies = 15)

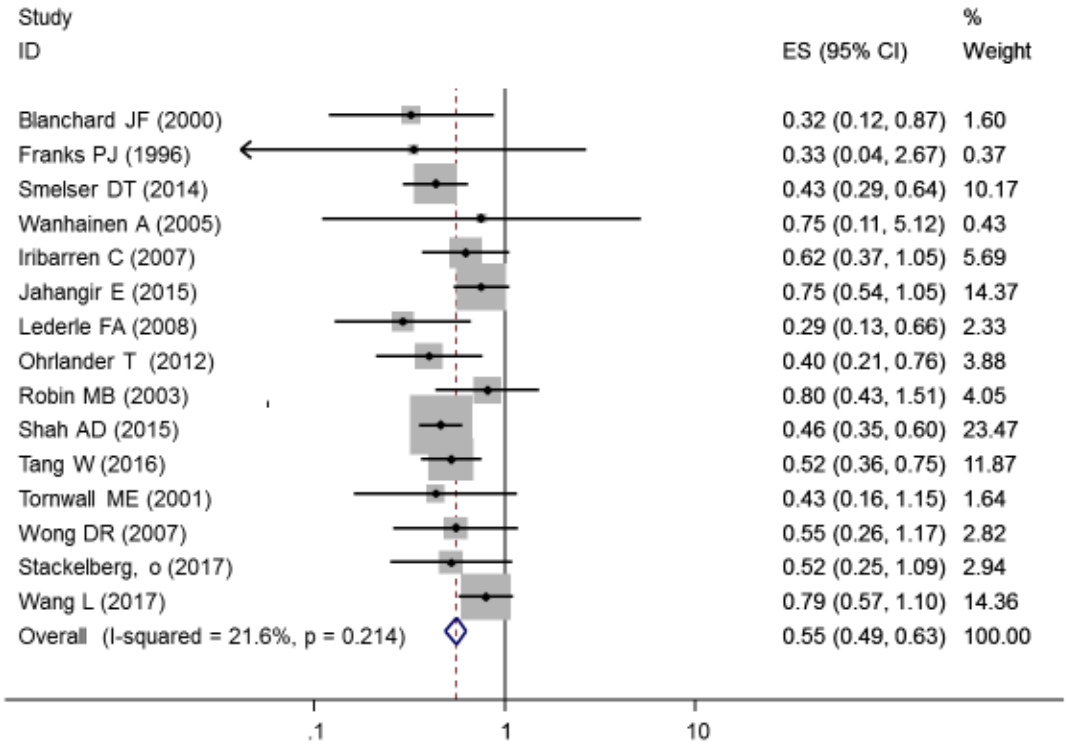


Figure 5.18 Relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a fixed-effects model by removing studies with no clear exclusion of type 1 diabetes (n studies = 2)

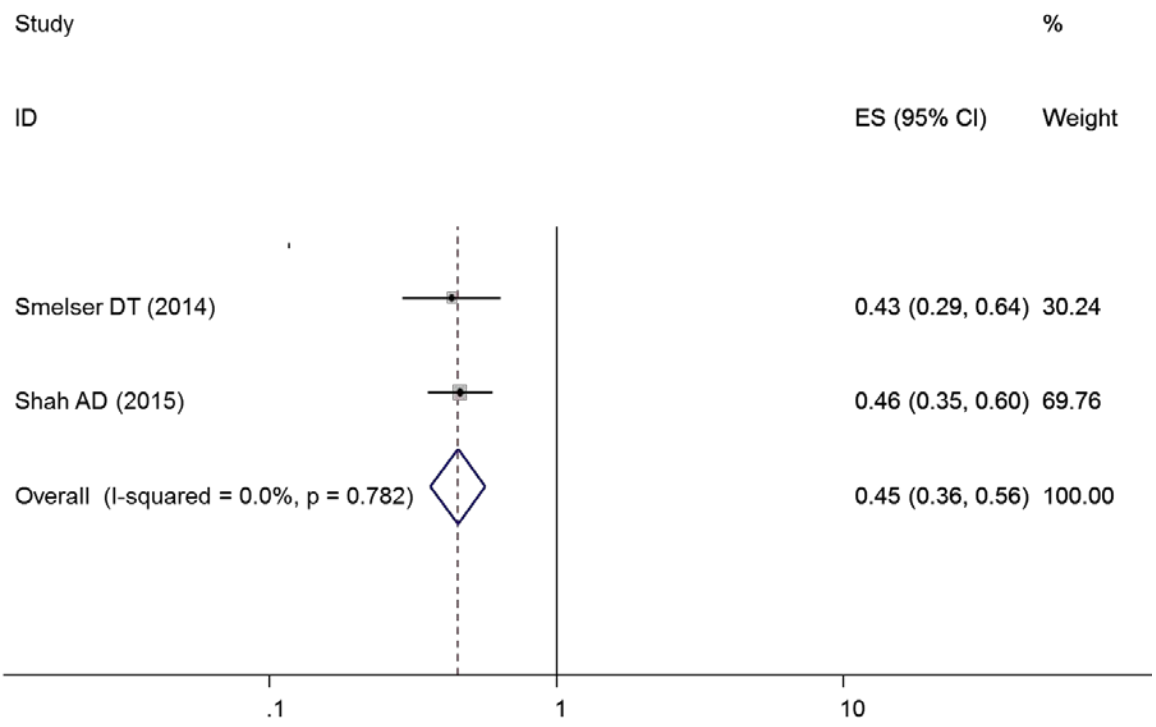


Figure 5.19 Relative risk (95% confidence interval) of abdominal aortic aneurysm (AAA) in relation to diabetes (yes, no) using a fixed-effects model by removing studies where AAA was not ascertained using clinical records (n studies = 14)

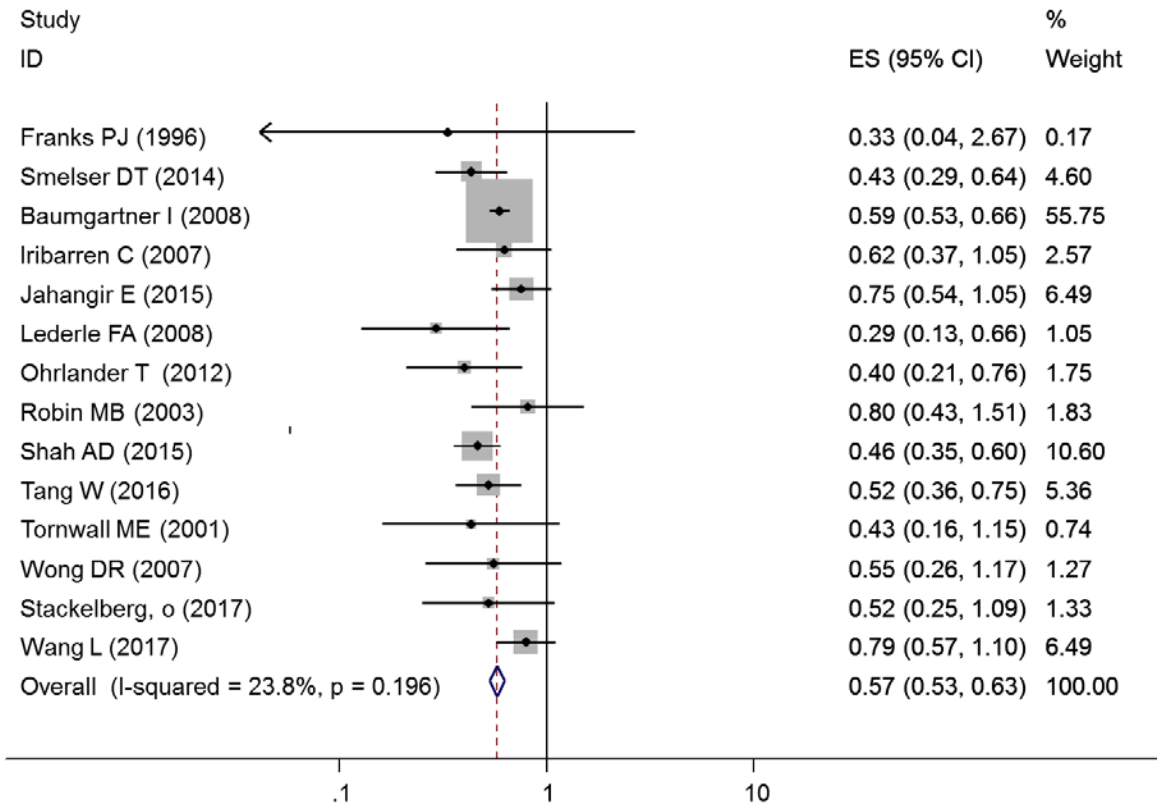


Figure 5.20 Relative risk (95% confidence interval) of abdominal aortic aneurysm (AAA) in relation to diabetes (yes, no) using a fixed-effects model by removing studies with insufficient follow up time (n studies = 11)

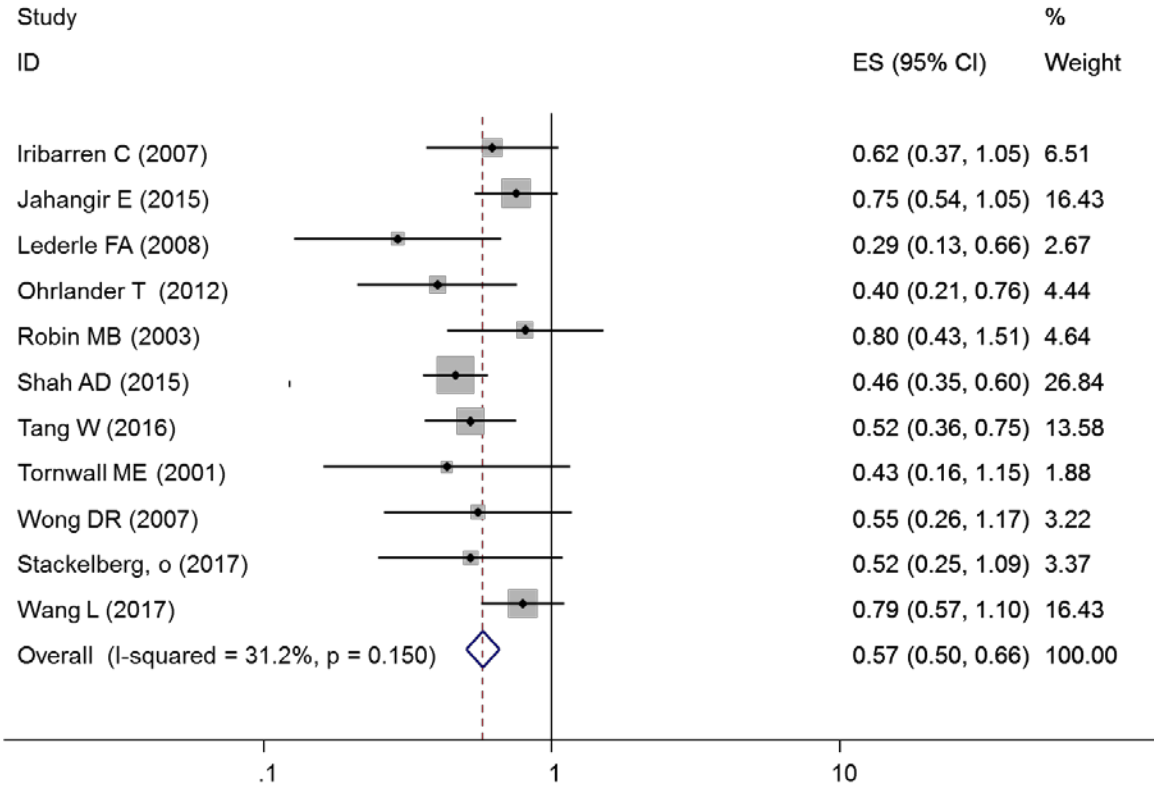


Figure 5.21 Relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a fixed-effects model by removing studies with inadequate adjustment (age, sex, race, and smoking; n studies = 9)

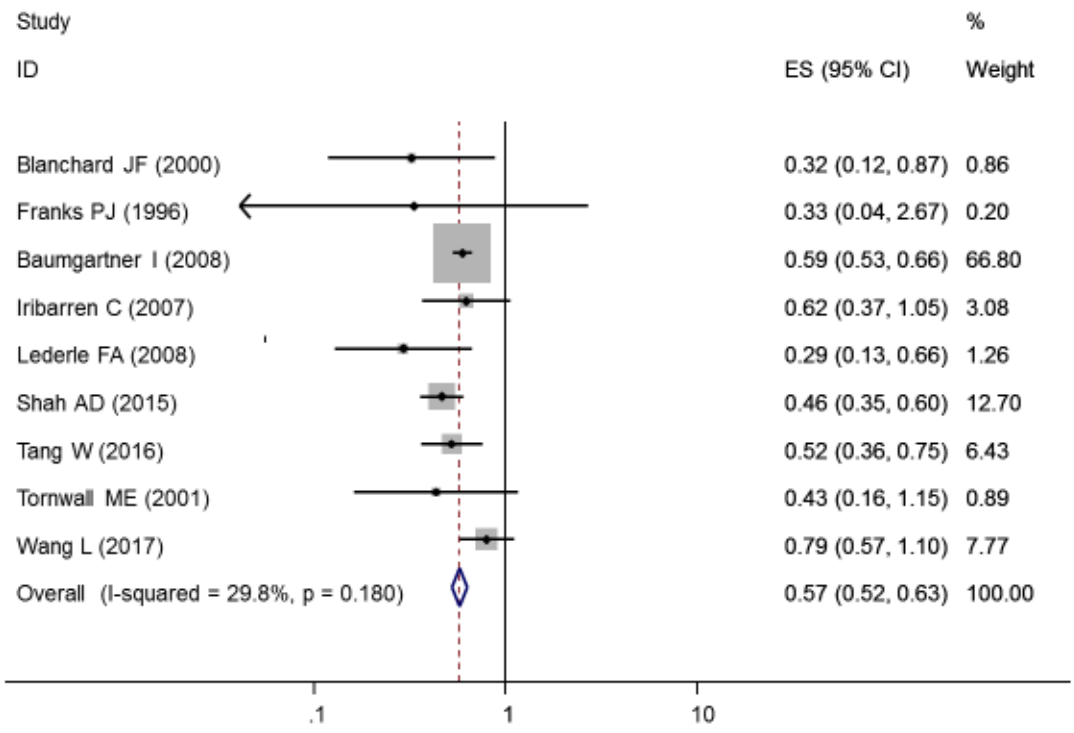


Figure 5.22 Relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a fixed-effects model by removing studies with low and moderate overall study quality (Newcastle-Ottawa score ≤ 5) (n studies = 12)

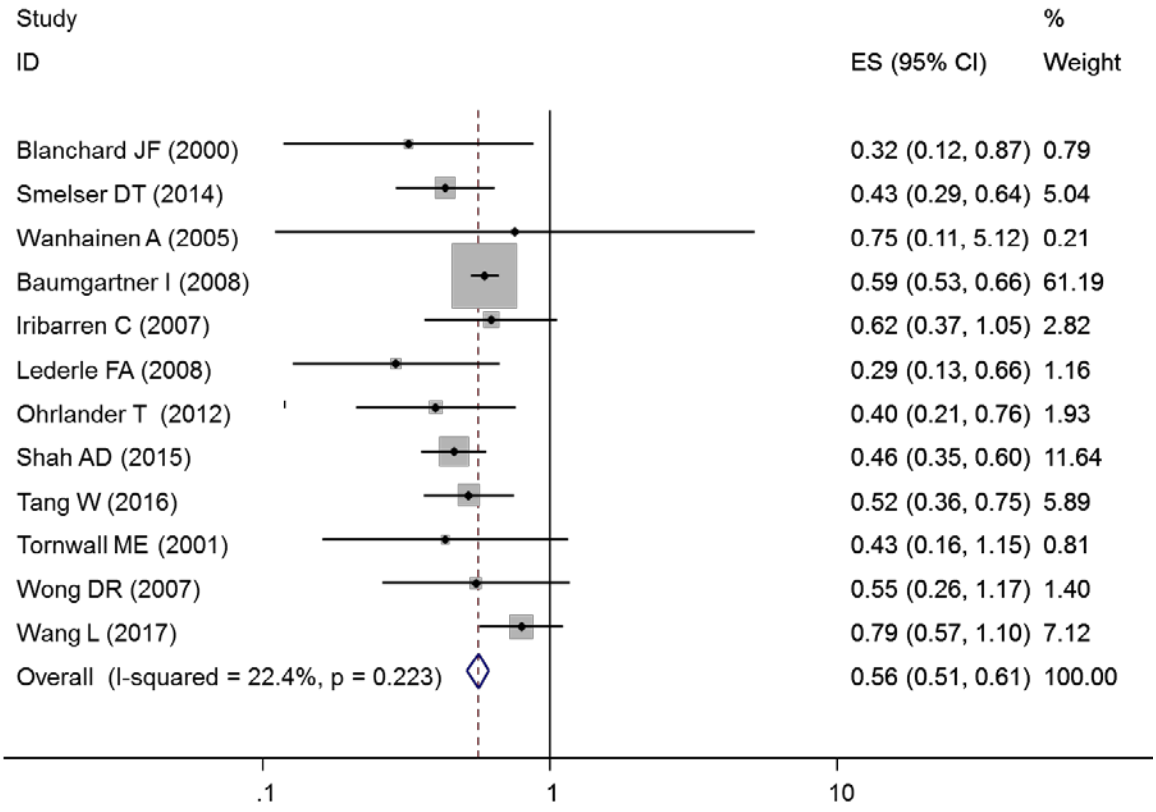


Figure 5.23 Pooled relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) (n = 16 studies) using a fixed-effects model by study design (cohort/case-control)

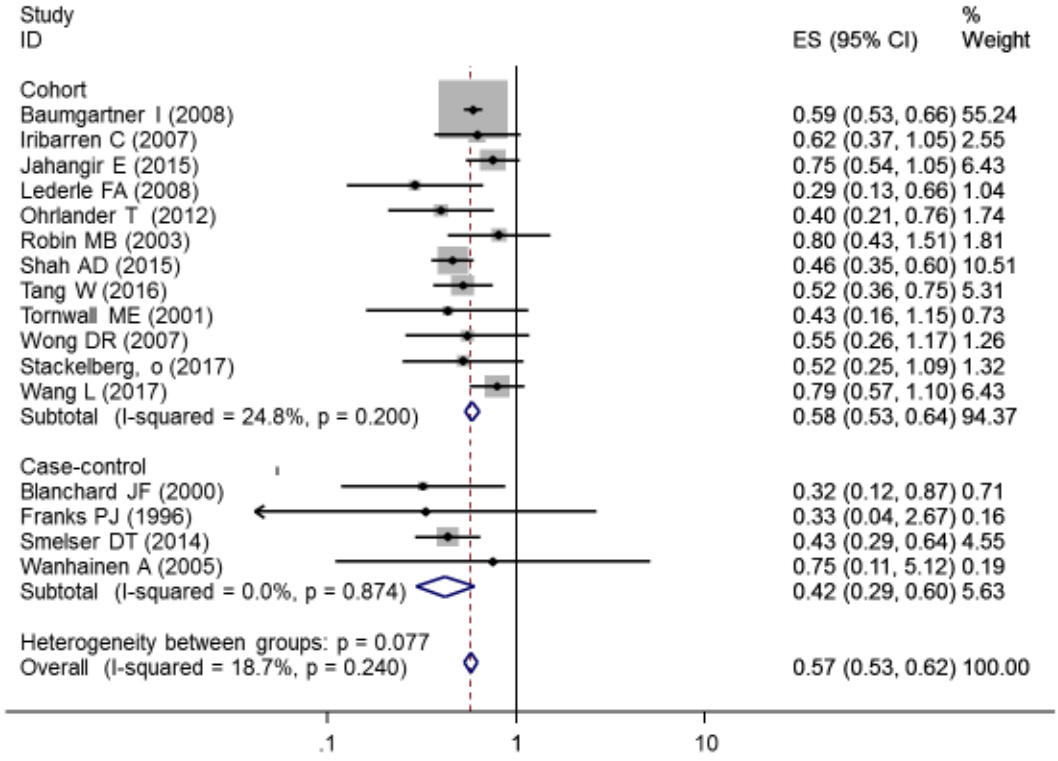


Figure 5.24 Pooled relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) (n = 16 studies) using a fixed-effects model by setting (clinical/population)

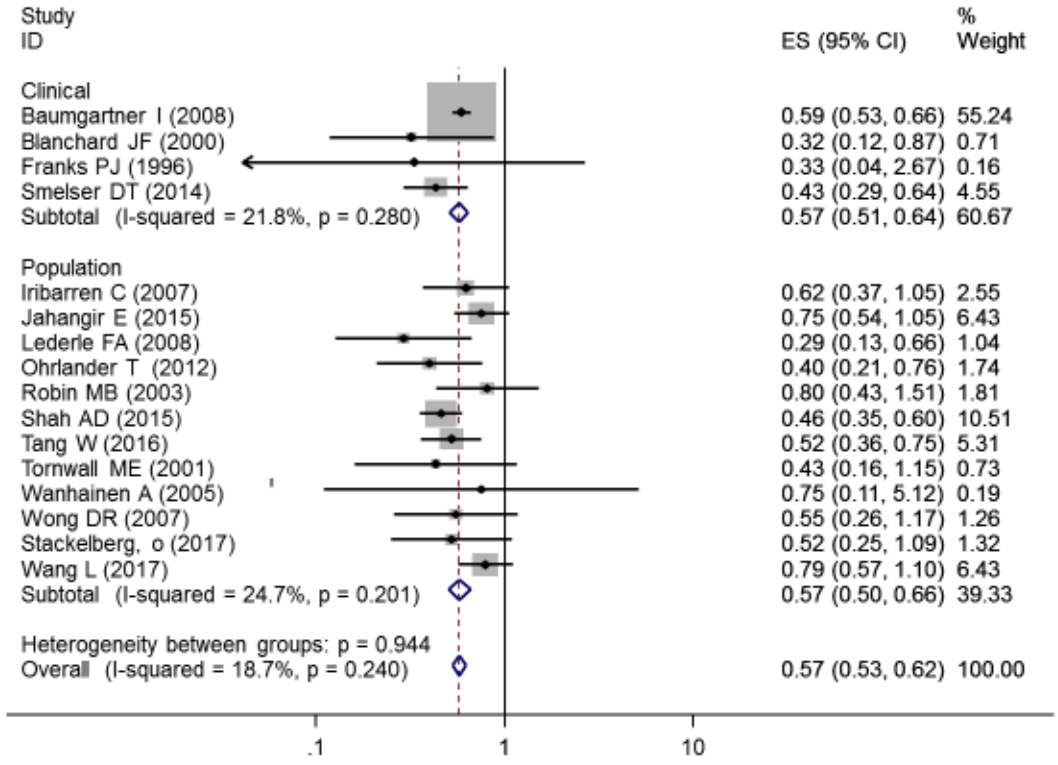


Figure 5.25 Pooled relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a fixed-effects model among men (n = 7 studies)

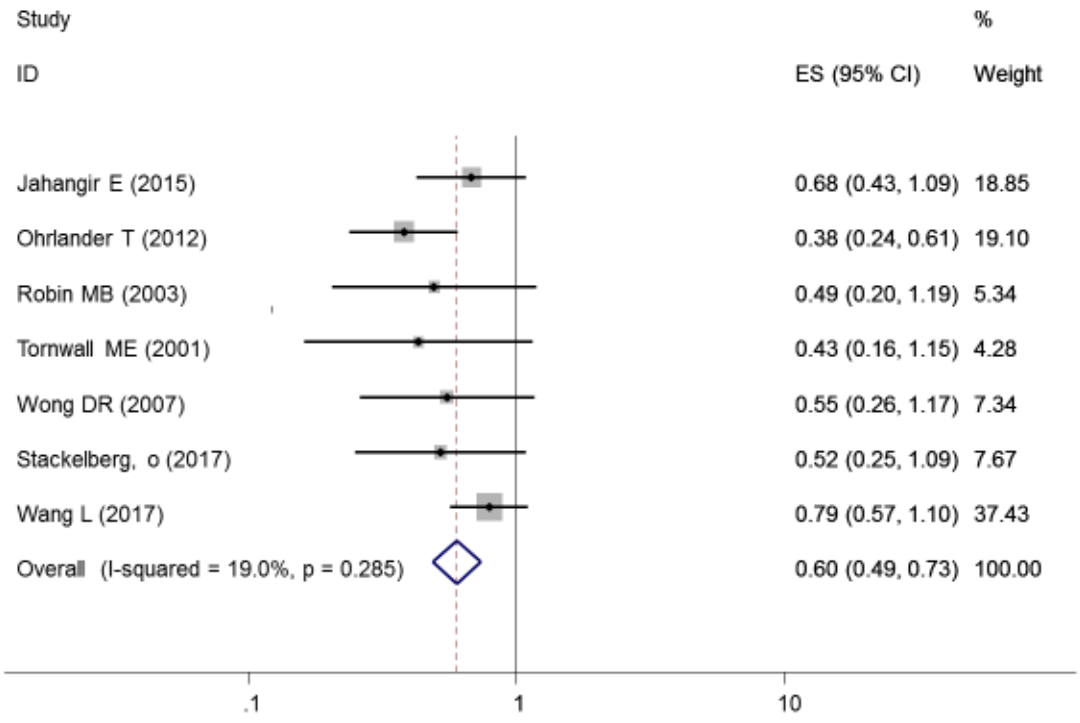
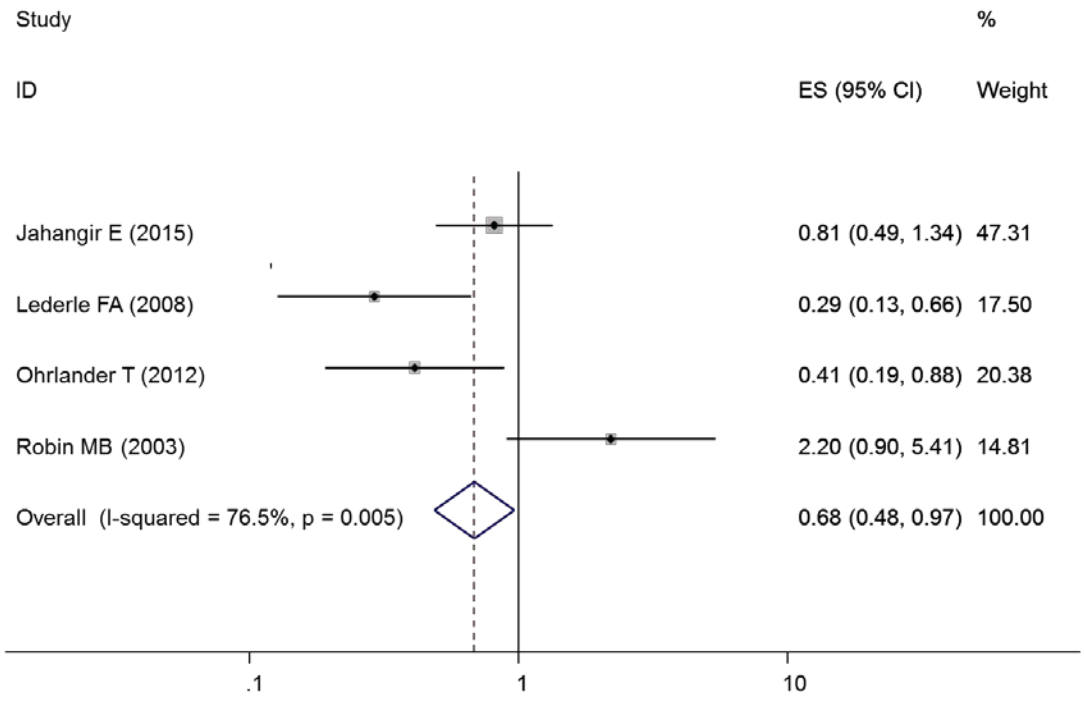


Figure 5.26 Pooled relative risk (95% confidence interval) of abdominal aortic aneurysm in relation to diabetes (yes, no) using a fixed-effects model among women (n = 4 studies)



Chapter 6. Summary

AAA is an important public health problem. The etiology of AAAs is not fully understood. Several risk factors for AAA, except for being free of diabetes, are well-known risk factors for atherosclerosis and atherosclerotic cardiovascular disease, but the relation between AAA and atherosclerosis is unclear. Previous findings also warrant us to further investigate the possible relation between diabetes and AAA.

In addition, an AAA is usually defined as an IAD ≥ 3 cm, but this is not a uniform definition, and an increased IAD from 2.3 to 3.0 cm has also been related to higher risk of being an AAA as well as other cardiovascular events. Thus, examining the determinants of IAD even among individuals whose IAD is smaller than 3 cm is potentially important to the prevention of AAAs. However, data on risk factors for an elevated IAD (≥ 2.2 cm) is limited.

The overall objectives of this dissertation were to fill a gap of literature and further assess AAA etiology by completing the following specific aims 1) examine the association of carotid atherosclerosis and stiffness with AAA occurrence, 2) explore the risk factors for elevated IAD among persons without an AAA, and 3) perform a systematic review and meta-analysis to quantify the association between diabetes mellitus and AAA. The ultimate goal is to improve the prevention, particularly early prevention, of AAAs at the population level. Findings from my dissertation studies may have potential to clinically identify high risk individuals. The summary of each manuscript is below.

6.1 Manuscript 1 Summary

Individuals with generalized atherosclerosis and arterial stiffness often have increased abdominal aortic diameters, but prospective evidence linking them to the risk of AAA is limited. In Manuscript 1, we prospectively examined the relationship of carotid atherosclerosis and stiffness with future risk of AAA in ARIC. At Visits 1 (1987-89) or 2 (1990-92), we assessed carotid atherosclerosis (represented by greater cIMT or presence of atherosclerotic plaque) and lower carotid distensibility (reflected by a higher carotid Beta Index). We identified incident, clinical AAAs during follow-up through 2011 using hospital discharge codes, Medicare outpatient diagnoses, or death certificates. Participants' mean age at baseline was 54.2 years (SD 5.8), 45% were male and 73% white. During a median of 22.5 years of follow-up, 542 clinical AAAs were ascertained. After multivariable adjustment, the presence of carotid atherosclerotic plaque at baseline was associated with 1.31 (95% CI: 1.10 - 1.57; P = 0.003) times higher risk of clinical AAA. Greater cIMT and Beta Index were also associated with clinical AAA with a dose-response across quartiles (P trend for both: 0.006; hazard ratios [95% CI] for the highest vs. lowest quartiles: 1.55 [1.13 - 2.11] and 1.68 [1.16 - 2.43], respectively). The associations of cIMT and Beta Index with AAA were independent of each other. Despite limitations summarized in **Chapter 3.4**, this prospective population-based study found that indices of greater carotid atherosclerosis and lower carotid distensibility are markers of increased AAA risk. In addition to a contribution to understanding AAA etiology, this study also has

clinical implications. For example, our study indicates that persons who have carotid atherosclerosis or who have ‘stiff’ carotid arteries may be high-risk for AAAs.

6.2 Manuscript 2 Summary

Although most of studies defined an AAA as an IAD ≥ 3 cm, an increased IAD over 2.3 - 3.0 cm has been associated with higher risk of AAA as well as other cardiovascular events. Data regarding the correlates of elevated IAD in the absence of AAA are sparse. In Manuscript 2, we examined the relationship between AAA risk factors and elevated IAD among ARIC participants who attended an abdominal ultrasound screening in 2011 - 13, after excluding those with prior AAAs by clinical records or the ultrasound exam. Weighted general estimating equation models were used to examine the relationships between the cumulative risk factors (across 1987 - 2013) and the odds of elevated IAD, defined as being in the highest quartile of the IAD distribution (2.2 cm ≤ IAD < 3.0 cm). Of 5,620 participants included in the analysis, 40.4% were men and 77.8% were whites. In the model with adjustment for AAA risk factors, men (vs. women) had 2.50 (95% CI: 1.90, 3.28) times higher odds, and participants with long-term diabetes (vs. non-diabetics) had 0.52 (95% CI: 0.35, 0.77) times lower odds of having an elevated IAD. Height, waist circumference and smoking pack-years were positively associated with elevated IADs [ORs (95% CI) for the highest vs. lowest quintiles of each risk factor: 1.93 (1.36, 2.75), 1.67 (1.28, 2.19) and 1.62 (1.26, 2.08), respectively). Other factors were not associated with elevated IAD.

In summary, male sex, smoking, greater height, larger waist circumference and diabetes were associated with elevated IAD among persons without an AAA. Despite limitations described in the limitation section of **Chapter 4.4**, the findings highlight the potential for primary prevention of AAA through control of these factors.

6.3 Manuscript 3 Summary

Literature regarding the relationship between diabetes and AAA are inconsistent across studies: some studies showed an inverse relationship while others did not show an association. We conducted a meta-analysis to examine the association between diabetes and AAA based on published data from case-control and prospective cohort studies. We searched literature in English from online databases, including MEDLINE (1966 -), EMBASE, and Web of Science as of Febuary 2018. In addition, we did a manual examination of references in selected articles. The eligibility criteria included: (1) a case-control or prospective cohort study conducted in adults; (2) diabetes was the exposure variable and AAA was the outcome variable; and (3) association estimates (hazard ratios, odds ratios, or relative risks) and measurement of variance (P value, confidence interval, or standard error) were available. A DerSimonian and Laird random effects model was used to pool association estimates and their 95% confidence intervals from studies. We included a total of 12 cohort studies with 11,410 AAAs in 2,665,121 participants and 4 case-control studies with 1,065 AAAs and 12,074 controls that met the pre-determined eligibility criteria in the meta-analyses. The

study populations were predominantly white (88%). Diabetes was inversely associated with the risk of AAA (pooled relative risk: 0.56; 95% confidence interval: 0.50 - 0.63). Results were similar in the subgroup analyses by sex (male/female), setting (population/clinical), and study design (cohort/case-control). In summary, in contrast with diabetes being a risk factor for most cardiovascular diseases, diabetes appears to be strongly and inversely associated with the risk of AAA. Future studies are warranted to investigate the potential mechanisms.

6.4 Overall Conclusions

This dissertation reports the relation between carotid atherosclerosis/ stiffness and diabetes with AAA occurrence, and the association between AAA risk factors and elevated IAD among persons without AAA. Future studies are needed to investigate the potential mechanisms mediating these associations. It is noteworthy that the dissertation research may be insufficient to establish causal relationship because these are all observational studies or a meta-analysis of observational studies. Nonetheless, we believe this information contributed to understanding of AAA etiology, and may be useful in formulating strategies for the prevention of AAA occurrence.

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